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☐	L38	L37 and anti-IGF-IR	1
☐	L37	424/178.1.ccls.	1172
☐	L36	L35 and anti-IGF-IR	8
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☐	L34	L33 and anti-IGF-IR	0
☐	L33	424/135.1-136.1.ccls.	273
☐	L32	L31 and (insulin)adj(like)adj(receptor)	0
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☐	L28	L27 and anti-IGF-IR	0
☐	L27	424/130.1.ccls.	1752
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☐	L25	530/391.3.ccls.	804
☐	L24	L23 and anti-IGF-IR	7
☐	L23	530/388.22.ccls.	1647
☐	L22	L21 and anti-IGF-IR	1
☐	L21	530/387.3.ccls.	1478
☐	L20	L18 and (human)adj(insulin)adj(like)adj(receptor)adj(1)	0
☐	L19	L18 and IGF-IR	0
☐	L18	530/387.1.ccls.	2386
☐	L17	anti-IGF-IR	53
☐	L16	(human)adj(insulin)adj(like)adj(growth)adj(factor)adj(receptor)	15
☐	L15	(human)adj(insulin)adj(like)adj(growth)adj(factor)adj(receptor)same (antibod?)	0
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☐	L13	(haeuw)adj(jean)adj(francois)	15
☐	L12	(duflos)adj(alain)	13

☐	L11	L10 and IGF-IR	4
☐	L10	(leger)adj(olivier)	14
☐	L9	L8 and anti-IGF-IR	3
☐	L8	(corvaia)adj(nathalie)	23
☐	L7	(goetsch)adj(liliane)	15
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☐	L5	5935821.pn.	1
☐	L4	5891996.pn.	1
☐	L3	6815540.pn.	1
☐	L2	5562903.pn.	1
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☐	L1	(antibod?)same(human)adj(IGF-IR)	18

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L2 1 L1 AND HUMAN INSULIN-LIKE GROWTH FACTOR RECEPTOR I

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L2 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
2003:951153 Document No. 140:26911 Human insulin-like growth factor receptor-specific human neutralizing monoclonal **antibodies** for treating and preventing cancer. Wang, Yan; Greenberg, Robert; Presta, Leonard; Pachter, Jonathan A.; Hailey, Judith; Brams, Peter; Williams, Denise; Srinivasan, Mohan; Feingersh, Diane (Schering Corporation, USA). PCT Int. Appl. WO 2003100008 A2 20031204, 144 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, US, UZ, VC, VN, YU, ZA, ZM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US16283 20030522. PRIORITY: US 2002-2002/PV38345U 20020524; US 2002-2002/PV39321U 20020702; US 2002-2002/PV436254 20021223.
AB The present invention includes transgenic non-human animal-produced fully human, neutralizing, monoclonal **antibodies** against **human insulin-like growth factor receptor-I** or IGFR1. The **antibodies** are useful for treating or preventing cancer in a subject. Also included are methods of using and producing the **antibodies** of the invention.

=> s l1 and human insulin-like growth factor I receptor
L3 66 L1 AND HUMAN INSULIN-LIKE GROWTH FACTOR I RECEPTOR

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L4 ANSWER 1 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
2005:1200829 Document No. 143:458527 **Antibodies** to the **human insulin-like growth factor I receptor** (IGF-IR) and/or to insulin/IGF-I hybrid receptors and anticancer and diagnostic uses thereof. Goetsch, Liliane; Corvaia, Nathalie; Duflos, Alain; Haeuw, Jean-Francois; Leger, Olivier; Beck, Alain (Pierre Fabre Medicament, Fr.). U.S. Pat. Appl. Publ. US 2005249730 A1 20051110, 144 pp., Cont.-in-part of U.S. Ser. No. 735,916. (English). CODEN: USXXCO. APPLICATION: US 2004-12353 20041216. PRIORITY: FR 2002-654 20020118; FR 2002-653 20020118; FR 2002-5753 20020507; WO 2003-FR178 20030120; FR 2003-8538 20030711; US 2003-2003/735916 20031216.
AB The present invention relates to novel **antibodies** capable of binding specifically to the **human insulin-like growth factor I receptor** (IGF-IR) and/or the insulin/IGF-I hybrid receptor (hybrid-R) and/or capable of

specifically inhibiting the tyrosine kinase activity of said IGF-IR and/or hybrid-R, especially monoclonal **antibodies** of murine, chimeric and humanized origin, as well as the amino acid and nucleic acid sequences coding for these **antibodies.** Provided are protein and cDNA sequences for anti-IGF-IR and/or anti-insulin/IGF-I hybrid receptors **antibodies.** The invention likewise comprises the use of these **antibodies** as a medicament for the prophylactic and/or therapeutic treatment of cancers overexpressing IGF-IR and/or hybrid-R or any pathol. connected with the overexpression of said receptor as well as in processes or kits for diagnosis of illnesses connected with the overexpression of the IGF-IR and/or hybrid-R. The invention finally comprises products and/or compns. comprising such **antibodies** in combination with anti-EGFR **antibodies** and/or compds. and/or anti-cancer agents or agents conjugated with toxins and their use for the prevention and/or the treatment of certain cancers.

L4 ANSWER 2 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
2005:346710 Document No. 142:390956 **Antibodies** to insulin-like growth factor I receptor. Goetsch, Liliane; Corvaia, Nathalie; Leger, Olivier; Duflos, Alain; Haeuw, Jean-francois; Beck, Alain (Fr.). U.S. Pat. Appl. Publ. US 2005084906 A1 20050421, 125 pp., Cont.-in-part of Appl. No. PCT/FR03/00178. (English). CODEN: USXXCO. APPLICATION: US 2003-735916 20031216. PRIORITY: FR 2002-654 20020118; FR 2002-653 20020118; FR 2002-5753 20020507; WO 2003-FR178 20030120; FR 2003-8538 20030711.
AB The authors disclose **antibodies** capable of binding specifically to the **human insulin-like growth factor I receptor** (IGF-IR) and/or capable of specifically inhibiting the IGF-IR tyrosine kinase activity. The monoclonal **antibodies** are of murine, chimeric and humanized origin **antibodies** and can be used as a medicament for the prophylactic and/or therapeutic treatment of cancers overexpressing IGF-IR or any pathol. connected with the IGF-IR overexpression. Addnl., the authors disclose the use of these **antibodies** in combination with anti-EGFR **antibodies** and/or anti-cancer agents or agents conjugated with toxins and their use for the prevention and/or the treatment of certain cancers.

L4 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
2005:182087 Document No. 142:278741 Single-chain **antibodies** against **human insulin-like growth factor I receptor** for inhibiting hormone-dependent tumor growth. Fujita-Yamaguchi, Yoko (City of Hope, USA). U.S. Pat. Appl. Publ. US 2005048050 A1 20050303, 19 pp., Cont.-in-part of U.S. Ser. No. 134,519. (English). CODEN: USXXCO. APPLICATION: US 2004-864818 20040610. PRIORITY: US 2000-2000/PV21118U 20000613; US 2000-2000/609776 20000703; US 2002-2002/134519 20020430.
AB A method of inhibiting the growth of hormone-dependent tumor cells in a mammal comprises administering to said mammal an insulin-like growth factor receptor (IGF-IR) recombinant **antibody**, wherein said **antibody** can be a single-chain recombinant **antibody**, which can be humanized, capable of blocking agonist interaction with the IGF-IR.

L4 ANSWER 4 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
2005:1260044 Document No. 144:35180 Insulin-like Growth Factor-I Receptor/Human Epidermal Growth Factor Receptor 2 Heterodimerization Contributes to Trastuzumab Resistance of Breast Cancer Cells. Nahta, Rita; Yuan, Linda X. H.; Zhang, Bing; Kobayashi, Ryuji; Esteva, Francisco J. (Departments of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA). Cancer Research, 65(23), 11118-11128 (English) 2005. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.
AB The majority of breast cancer patients who achieve an initial therapeutic response to the human epidermal growth factor receptor 2 (HER-2)-targeted

antibody trastuzumab will show disease progression within 1 yr. The authors previously reported the characterization of SKBR3-derived trastuzumab-resistant pools. In the current study, the authors show that HER-2 interacts with insulin-like growth factor-I receptor (IGF-IR) uniquely in these resistant cells and not in the parental trastuzumab-sensitive cells. The occurrence of cross talk between IGF-IR and HER-2 exclusively in resistant cells is evidenced by the IGF-I stimulation resulting in increased phosphorylation of HER-2 in resistant cells, but not in parental cells, and by the inhibition of IGF-IR tyrosine kinase activity leading to decreased HER-2 phosphorylation only in resistant cells. In addition, inhibition of IGF-IR tyrosine kinase activity by I-OMe-AG538 increased sensitivity of resistant cells to trastuzumab. HER-2/IGF-IR interaction was disrupted on exposure of resistant cells to the anti-IGF-IR **antibody** α-IR3 and, to a lesser extent, when exposed to the anti-HER-2 **antibody** pertuzumab. Heterodimer disruption by α-IR3 dramatically restored sensitivity to trastuzumab and resistant cells showed a slightly increased sensitivity to pertuzumab vs. parental cells. Neither α-IR3 nor pertuzumab decreased HER-2 phosphorylation, suggesting that addnl. sources of phosphorylation other than IGF-IR exist when HER-2 and IGF-IR are not phys. bound. Our data support a unique interaction between HER-2 and IGF-IR in trastuzumab-resistant cells such that cross talk occurs between IGF-IR and HER-2. These data suggest that the IGF-IR/HER-2 heterodimer contributes to trastuzumab resistance and justify the need for further studies examining this complex as a potential therapeutic target in breast cancers that have progressed while on trastuzumab.

L4 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN

2005:508363 Document No. 143:456860 Role of insulin-like growth factor 1 receptor signalling in cancer. Larsson, O.; Girnita, A.; Girnita, L. (Department of Oncology and Pathology, Karolinska Hospital, Stockholm, S-171 76, Swed.). British Journal of Cancer, 92(12), 2097-2101 (English) 2005. CODEN: BJCAAI. ISSN: 0007-0920. Publisher: Nature Publishing Group.

AB A review. The insulin-like growth factor (IGF-1) signalling is highly implicated in cancer. In this signalling the IGF-1 receptor (IGF-1R) is unquestionable, the predominating single factor. IGF-1R is crucial for tumor transformation and survival of malignant cell, but is only partially involved in normal cell growth. This is in part due to the interactions with oncogenes. Recent findings suggest a close interplay with the p53/MDM2 pathway. Disturbances in components in the p53/MDM2/IGF-1R network may cause IGF-1R upregulation and growth advantage for the cancer cell. Targeting of IGF-1R is more and more seen as a promising option for future cancer therapy. Single chain **antibodies** and small mols. with selective effects on IGF-1R dependent malignant growth are of particular interest. Forthcoming clin. trials are welcome and will indeed be the only way to evaluate the impact of IGF-1R targeting in human cancer.

L4 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN

2005:340020 Document No. 143:364267 Insulin-like growth factor-I receptor activity is essential for Kaposi's sarcoma growth and survival. Catrina, S-B.; Lewitt, M.; Massambu, C.; Dricu, A.; Gruenler, J.; Axelson, M.; Biberfeld, P.; Brismar, K. (Department of Molecular Medicine, Diabetes Center Karolinska, Karolinska Institutet, M1:02, Karolinska Hospital, Stockholm, Swed.). British Journal of Cancer, 92(8), 1467-1474 (English) 2005. CODEN: BJCAAI. ISSN: 0007-0920. Publisher: Nature Publishing Group.

AB Kaposi's sarcoma (KS) is a highly vascular tumor and is the most common neoplasm associated with human immunodeficiency virus (HIV-1) infection. Growth factors, in particular vascular endothelial growth factor (VEGF), have been shown to play an important role in its development. The role of insulin-like growth factors (IGFs) in the pathophysiol. of different tumors led us to evaluate the role of IGF system in KS. The IGF-I receptors (IGF-IR) were identified by immunohistochem. in biopsies taken

from patients with different AIDS/HIV-related KS stages and on KSIMM cells (an established KS-derived cell line). Insulin-like growth factor-I is a growth factor for KSIMM cells with a maximum increase of 3H-thymidine incorporation of 130±27.6% ($P<0.05$) similar to that induced by VEGF and with which it is additive (281±13%) ($P<0.05$). Moreover, specific blockade of the receptor (either by α IR3 **antibody** or by picropodophyllin, a recently described selective IGF-IR tyrosine phosphorylation inhibitor) induced KSIMM apoptosis, suggesting that IGF-IR agonists (IGF-I and -II) mediate antiapoptotic signals for these cells. We were able to identify an autocrine loop essential for KSIMM cell survival in which IGF-II is the IGF-IR agonist secreted by the cells. In conclusion, IGF-I pathway inhibition is a promising therapeutical approach for KS tumors.

L4 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN

2004:696273 Document No. 141:205683 Therapeutic uses of human anti-**human insulin-like growth factor I receptor antibodies.**

Cohen, Bruce David; Bedian, Vahe; Wang, Huifen Faye; Obrocea, Mihail; Gomez-Navarro, Jesus; Cusmano, John Daniel; Guyot, Deborah Jean; Page, Kelly Lynn (Pfizer Products Inc., USA). PCT Int. Appl. WO 2004071529 A2 20040826, 105 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-IB366 20040203. PRIORITY: US 2003-2003/PV447353 20030213.

AB The present invention relates to a therapeutic method comprising administering anti-**human insulin-like growth factor I receptor** (IGF-IR) **antibodies**, particularly fully human anti-IGF-IR **antibodies** to a subject for the treatment of certain disorders, such as cancer, preferably in conjunction with administration of another therapeutic agent. In preferred embodiment anti-IGF-IR **antibodies** comprise heavy chain from the human VH DP-35, VIV-4/4.35, VH DP-47, or VH DP-71 gene, and light chain from the A27, A30, or 012 gene. The invention further relates to pharmaceutical compns. comprising these **antibodies** and methods of using the **antibodies** and compns. thereof for treatment. Demonstrated that the **antibodies** of the invention are able to target the IGF-IR in vivo and in vitro. Also demonstrated that a single treatment with antiboy 2.13.2 alone inhibited the growth of IGF-IR transfected NIH-3T3 cell-induced tumors.

L4 ANSWER 8 OF 33 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2005:22256 Document No.: PREV200500021797. The expression of insulin-like growth factor-I receptor correlates with Fuhrman grading of renal cell carcinomas. Ahmad, Nazeel; Keehn, Connie A.; Coppola, Domenico [Reprint Author]. CytoCor Diagnost Lab Serv, 10421 Univ Ctr Dr,Suite 500, Tampa, FL, 33612, USA. Human Pathology, (September 2004) Vol. 35, No. 9, pp. 1132-1136. print.

ISSN: 0046-8177 (ISSN print). Language: English.

AB Recent reports have shown significant correlation between Fuhrman nuclear grade of renal cell carcinoma (RCQ and patient survival. However, no one specific gene alteration has yet been described to account for this correlation. This study investigated the expression of the insulin-like growth factor-I receptor (IGF-IR) in RCC and correlated the results to the tumor Fuhrman nuclear grade. Formalinfixed, paraffin-embedded sections from 68 cases of RCC were stained using the immunohistochemical avidin-biotin-peroxidase method. An anti-human IGF-IR rabbit polyclonal **antibody** was used. The stains were semiquantitatively evaluated

using the Allred score system, assessing intensity of stain and percentage of positive tumor cells. Statistical analysis was performed using the Kruskal-Wallis test. Strong and diffuse cytoplasmic IGF-IR stain (Allred score 7 to 8) was identified in 25 of 25 (100%) of grade 3 and 4 RCCs. Grade 2 RCCs had a median IGF-IR Allred score of 4. Ten of 10 (100%) grade 1RCCs were negative. Even in the positive high-nuclear-grade tumors, areas of low nuclear grade, when present, were IGF-IR negative. Statistical analysis using the Kruskal-Wallis test demonstrated significant correlation between increasing Fuhrman nuclear grade and increasing IGF-IR Allred score ($P<0.0001$). Thus we report the novel finding of significant statistical correlation between IGF-IR protein expression and Fuhrman nuclear grade of RCC, and consequentially with patient survival. HUM PATHOL 35:1132-1136.

L4 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
2003:571020 Document No. 139:132446 Monoclonal and humanized **antibodies** to insulin-like growth factor 1 receptors for use in the diagnosis and treatment of disease. Goetsch, Liliane; Corvaia, Nathalie; Leger, Olivier (Pierre Fabre Medicament, Fr.). PCT Int. Appl. WO 2003059951 A2 20030724, 164 pp. DESIGNATED STATES: W: AU, CA, CN, JP, MX, US, ZA; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (French). CODEN: PIXXD2. APPLICATION: WO 2003-FR178 20030120. PRIORITY: US 2002-2002/200653 20020118; US 2002-2002/200654 20020118; US 2002-2002/205753 20020507.
AB The invention relates to novel **antibodies** capable of binding specifically to the **human Insulin-like Growth Factor-I Receptor** (IGF-IR), in particular monoclonal of murine origin, chimeric and humanized as well as the amino and nucleic acid sequences coding for said **antibodies**. The invention also concerns the use of said **antibodies** as medicine for prophylactic and/or therapeutic treatments of cancers as well as methods or kit for diagnosis of diseases related to overexpression of the IGF-IR receptor. The invention further concerns products and/or compns. containing such **antibodies** combined with **antibodies** to epidermal growth factor receptors and/or compds. and/or anti-cancer agents or conjugates with toxins and their use for preventing and/or treating certain cancers.

L4 ANSWER 10 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
2003:696297 Document No. 139:212894 Single-chain **antibodies** against **human insulin-like growth factor I receptor**: expression, purification, and effect on tumor growth. Fujita-Yamaguchi, Yoko (City of Hope, USA). U.S. Pat. Appl. Publ. US 2003165502 A1 20030904, 12 pp., Cont. of U.S. Ser. No. 609,776, abandoned. (English). CODEN: USXXCO. APPLICATION: US 2002-134519 20020430. PRIORITY: US 2000-PV211187 20000613; US 2000-609776 20000703.
AB A method of inhibiting the growth of hormone dependent tumor cells in a mammal comprises administering to said mammal an insulin-like growth factor receptor (IGF-IR) recombinant **antibody**, wherein said **antibody** can be a single-chain recombinant **antibody**, which can be humanized, capable of blocking agonist interaction with the IGF-IR.

L4 ANSWER 11 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
2003:573239 Document No. 139:132447 Monoclonal and humanized **antibodies** to insulin-like growth factor 1 receptors for use in diagnosis and treatment of cancer. Goetsch, Liliane; Leger, Olivier; Corvaia, Nathalie (Pierre Fabre Medicament, Fr.). Fr. Demande FR 2834990 A1 20030725, 137 pp. (French). CODEN: FRXXBL. APPLICATION: FR 2002-653 20020118.
AB The invention relates to novel **antibodies** capable of binding specifically to the **human Insulin-like Growth Factor-I Receptor** (IGF-IR),

in particular monoclonal of murine origin, chimeric and humanized as well as the amino and nucleic acid sequences coding for said **antibodies** . The invention also concerns the use of said **antibodies** as medicine for prophylactic and/or therapeutic treatments of cancers as well as methods or kit for diagnosis of diseases related to overexpression of the IGF-IR receptor. The invention further concerns products and/or compns. containing such **antibodies** combined with **antibodies** to epidermal growth factor receptors and/or compds. and/or anti-cancer agents or conjugates with toxins and their use for preventing and/or treating certain cancers.

L4 ANSWER 12 OF 33 MEDLINE on STN DUPLICATE 1

2003402761. PubMed ID: 12941837. An anti-insulin-like growth factor I receptor **antibody** that is a potent inhibitor of cancer cell proliferation. Maloney Erin K; McLaughlin Jennifer L; Dagdigian Nancy E; Garrett Lisa M; Connors Katherine M; Zhou Xiao-Mai; Blattler Walter A; Chittenden Thomas; Singh Rajeeva. (ImmunoGen, Inc., 128 Sidney Street, Cambridge, Massachusetts 02139, USA.) Cancer research, (2003 Aug 15) 63 (16) 5073-83. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB An antagonistic monoclonal **antibody**, designated EM164, has been developed which binds specifically to the **human insulin -like growth factor I receptor** (IGF-IR) and inhibits the proliferation and survival functions of the receptor in cancer cells. EM164 was initially selected by a rapid cell-based screen of hybridoma supernatants to identify **antibodies** that bind to IGF-IR but not to the homologous insulin receptor and that show maximal inhibition of IGF-I-stimulated autophosphorylation of IGF-IR. EM164 binds tightly to IGF-IR with a dissociation constant K(d) of 0.1 nM, inhibits binding of IGF-I and antagonizes its effects on cells completely, and has no agonistic activity on its own. EM164 inhibits IGF-I-, IGF-II-, and serum-stimulated proliferation and survival of diverse human cancer cell lines in vitro, including breast, lung, colon, cervical, ovarian, pancreatic, melanoma, prostate, neuroblastoma, rhabdomyosarcoma, and osteosarcoma cancer lines. It also suppresses the autocrine or paracrine proliferation of several cancer cell lines. EM164 was the most potent antagonistic anti-IGF-IR **antibody** tested when compared with several commercially available **antibodies.** The in vitro inhibitory effect could be extended to in vivo tumor models, where EM164 caused regression of established BxPC-3 human pancreatic tumor xenografts in SCID mice. The antitumor effect of treatment with EM164 could be enhanced by combining it with the cytotoxic agent gemcitabine. These data support the development of EM164 as a candidate therapeutic agent that targets IGF-IR function in cancer cells.

L4 ANSWER 13 OF 33 MEDLINE on STN DUPLICATE 2

2004012516. PubMed ID: 14710368. Inhibition of the biologic response to insulin-like growth factor I in MCF-7 breast cancer cells by a new monoclonal **antibody** to the insulin-like growth factor-I receptor. The importance of receptor down-regulation. Jackson-Booth P-G; Terry C; Lackey B; Lopaczynska M; Nissley P. (Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892 USA.) Hormone and metabolic research. Hormon- und Stoffwechselforschung. Hormones et metabolisme, (2003 Nov-Dec) 35 (11-12) 850-6. Journal code: 0177722. ISSN: 0018-5043. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB We developed a mouse monoclonal **antibody** (4G11) against insulin-like growth factor I receptor by immunizing mice with mouse embryo fibroblasts overexpressing the **human insulin- like growth factor-I receptor.** Not only did the 4G11 **antibody** inhibit the binding of [(125)I]insulin-like growth factor-I to the fibroblast receptor, but 4G11 **antibody** also potently down-regulated the insulin-like growth factor-I receptor. 4G11 Fab fragment inhibited ligand binding, but did not down-regulate the receptor, suggesting that receptor

aggregation is required for down-regulation. 4G11 **antibody** also down-regulated the receptor in MCF-7 breast cancer cells, a panel of colon cancer cells and MG-63 osteosarcoma cells. Receptor recovery in MCF-7 cells after down-regulation by 4G11 **antibody** was slow, requiring 32 - 48 h for full recovery. Receptor down-regulation in MCF-7 cells by 4G11 **antibody** was confirmed by FACS analysis of intact and permeabilized cells. In contrast to 4G11 **antibody**, insulin-like growth factor-I did not down-regulate the receptor in MCF-7 cells. Down-regulation of the receptor by 4G11 **antibody** in MCF-7 cells resulted in inhibition of Akt and MAPK activation by insulin-like growth factor-I. We conclude that the ability of a monoclonal **antibody** to down-regulate the receptor may be an important **antibody** property in targeting the insulin-like growth factor-I receptor for the treatment of certain cancers.

L4 ANSWER 14 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
2002:521793 Document No. 137:77889 Human **antibodies** to insulin-like growth factor I receptor. Cohen, Bruce D.; Beebe, Jean; Miller, Penelope E.; Moyer, James D.; Corvalan, Jose R.; Gallo, Michael (Pfizer Inc., USA; Abgenix, Inc.). PCT Int. Appl. WO 2002053596 A2 20020711, 172 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US51113 20011220. PRIORITY: US 2001-2001/PV259927 20010105.

AB The authors disclose the preparation and characterization of **antibodies** that specifically bind to **human insulin-like growth factor I receptor** (IGF-IR). The **antibodies** were prepared by immunization of XenoMouse with either the extracellular domain of human IGF-IR or with cells transformed for surface expression of the receptor. The isolated **antibodies** were shown to down-regulate IGF-IR, to prevent its phosphorylation induced by ligand, and to exhibit tumor growth inhibitory activities either alone or in combination with chemotherapeutic agents.

L4 ANSWER 15 OF 33 MEDLINE on STN DUPLICATE 3
2000418704. PubMed ID: 10941907. Single-chain **antibodies** against **human insulin-like growth factor I receptor**: expression, purification, and effect on tumor growth. Li S L; Liang S J; Guo N; Wu A M; Fujita-Yamaguchi Y. (Department of Molecular Biology, Beckman Research Institute of the City of Hope, Duarte, CA 91010, USA.) Cancer immunology, immunotherapy : CII, (2000 Jul) 49 (4-5) 243-52. Journal code: 8605732. ISSN: 0340-7004. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Insulin-like growth factors (IGF) I and II are potent mitogens for a variety of cancer cells. The proliferative and anti-apoptotic actions of IGF are mediated by the IGF-I receptor (IGF-IR), to which both IGF-I and IGF-II bind with high affinity. To investigate the mitogenic and anti-apoptotic activities of IGF-IR and to achieve better inhibition of IGF-IR function, single-chain **antibodies** against human IGF-IR (alphaIGF-IR scFvs) were constructed and expressed. IgG cDNA encoding variable regions of light and heavy chains (VL and VH) from mouse IgG were cloned from a hybridoma producing the 1H7 alphaIGF-IR monoclonal **antibody** [Li et al., Biochem Biophys Res Commun 196: 92-98 (1993)]. The splice-overlap extension polymerase chain reaction was used to assemble a gene encoding the alphaIGF-IR scFv, including the N-terminal signal peptide, VL, linker peptide, VH, and C-terminal DYKD tag. Two types of soluble alphaIGF-IR scFvs, a prototype alphaIGF-IR scFv and its alternative type alphaIGF-IR scFv-Fc, were constructed and expressed in

murine myeloma cells. alphaIGF-IR scFv-Fc, containing the human IgG1 Fc domain, was stably expressed in NS0 myeloma cells, using a glutamine synthase selection system, and purified from the conditioned medium of stable clones by protein-A--agarose chromatography. Levels of alphaIGF-IR scFv-Fc expression ranged from 40 mg/l to 100 mg/l conditioned medium. Sodium dodecyl sulfate/polyacrylamide gel electrophoresis analysis under reducing and nonreducing conditions indicated that alphaIGF-IR scFv-Fc is a dimeric **antibody.** alphaIGF-IR scFv-Fc retained general characteristics of the parental 1H7 monoclonal **antibody** except that its binding affinity for IGF-IR was estimated to be approximately 10(8) M(-1), which was one-order of magnitude lower than that of 1H7 monoclonal **antibody.** Injection of alphaIGF-IR scFv-Fc (500 microg/mouse, twice a week) significantly suppressed MCF-7 tumor growth in athymic mice. These results suggest that the alphaIGF-IR scFv-Fc is a first-generation recombinant alphaIGF-IR for the potential development of future alphaIGF-IR therapeutics.

L4 ANSWER 16 OF 33 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2000:25421 Document No.: PREV200000025421. Single chain **antibodies** against **human insulin-like growth factor-I receptor**: Inhibition of MCF-7 breast tumor growth in vivo. Fujita-Yamaguchi, Y. [Reprint author]; Liang, S.-J. [Reprint author]; Guo, N. [Reprint author]; Wu, A. M. [Reprint author]; Li, S.-L. [Reprint author]. Beckman Research Institute of City of Hope, Duarte, CA, USA. Growth Hormone and IGF Research, (Oct., 1999) Vol. 9, No. 5, pp. 334-335. print.
Meeting Info.: 5th International Symposium on Insulin-Like Growth Factors. Brighton, England, UK. October 31-November 4, 1999. Growth Hormone Research Society.
ISSN: 1096-6374. Language: English.

L4 ANSWER 17 OF 33 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1997:261790 The Genuine Article (R) Number: WQ635. Characterization of ligand binding of a soluble **human insulin-like growth factor I receptor** variant suggests a ligand-induced conformational change. Jansson M (Reprint); Hallen D; Koho H; Andersson G; Berghard L; Heidrich J; Nyberg E; Uhlen M; Kordel J; Nilsson B. PHARM & UPJOHN AB, PRECLIN RES, S-11287 STOCKHOLM, SWEDEN; ROYAL INST TECHNOL, DEPT BIOCHEM & BIOTECHNOL, S-10044 STOCKHOLM, SWEDEN. JOURNAL OF BIOLOGICAL CHEMISTRY (28 MAR 1997) Vol. 272, No. 13, pp. 8189-8197. ISSN: 0021-9258. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Details of the signal transduction mechanisms of the tyrosine kinase family of growth factor receptors remain elusive. In this work, we describe an extensive study of kinetic and thermodynamic aspects of growth factor binding to a soluble extracellular **human insulin-like growth factor-I receptor** (sIGF-I-R) variant. The extracellular receptor domains were produced fused to an IgG-binding protein domain (Z) in transfected human 293 cells as a correctly processed secreted alpha-beta'-Z dimer. The receptor was purified using IgG affinity chromatography, rendering a pure and homogenous protein in yields from 1 to 5 mg/liter of conditioned cell media. Biosensor technology (BIAcore) was applied to measure the insulin-like growth factor-I (IGF-I), des(1-3)IGF-I, insulin-like growth factor-II, and insulin ligand binding rate constants to the immobilized IGF-I-R-Z. The association equilibrium constant, K-a for the IGF-I interaction is determined to 2.8 x 10(8) M(-1) (25 degrees C). Microcalorimetric titrations on IGF-I/IGF-I-R-Z were performed at three different temperatures (15, 25, and 37 degrees C) and in two different buffer systems at 25 degrees C. From these measurements, equilibrium constants for the 1:1 (IGF-I:(alpha-beta'-Z)(2)) receptor complex in solution are deduced to 0.96 x 10(8) M(-1) (25 degrees C). The determined

heat capacity change for the process is large and negative, -0.51 kcal (K mol)(-1). Further, the entropy change (Delta S) at 25 degrees C is large and negative. Far- and near-UV circular dichroism measurements display significant changes over the entire wavelength range upon binding of IGF-I to IGF-I-R-Z. These data are all consistent with a significant change in structure of the system upon IGF-I binding.

L4 ANSWER 18 OF 33 MEDLINE on STN DUPLICATE 4

96216359. PubMed ID: 8621681. Characterization and cloning of a 58/53-kDa substrate of the insulin receptor tyrosine kinase. Yeh T C; Ogawa W; Danielsen A G; Roth R A. (Department of Molecular Pharmacology, Stanford University School of Medicine, Stanford, California 94305, USA.) Journal of biological chemistry, (1996 Feb 9) 271 (6) 2921-8. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB A monoclonal **antibody** has been produced which immunoprecipitates 58- and 53-kDa proteins which are rapidly tyrosine phosphorylated in insulin-treated cells. These proteins can also be tyrosine phosphorylated in vitro by the isolated human insulin receptor. Increased tyrosine phosphorylation of these proteins is also observed in cells expressing a transforming chicken c-Src (mutant Phe-527) and in cells with the activated tyrosine kinase domains of the Drosophila insulin receptor, **human insulin-like growth factor I receptor**, and human insulin receptor-related receptor. P58/53 did not appear to associate with either the GTPase activating protein of Ras (called GAP) or the phosphatidylinositol 3-kinase by either co-immunoprecipitation experiments or in Far Westerns with the SH2 domains of these two proteins. Since p58/53 did not appear, by immunoblotting, to be related to any previously described tyrosine kinase substrate such as the SH2 containing proteins SHC and the tyrosine phosphatase Syp, the protein was purified in sufficient amounts to obtain peptide sequence. This sequence was utilized to isolate a cDNA clone that encodes a previously uncharacterized 53-kDa protein which, when expressed in mammalian cells, is tyrosine phosphorylated by the insulin receptor.

L4 ANSWER 19 OF 33 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1995:523277 The Genuine Article (R) Number: RN954. INSULIN-LIKE GROWTH-FACTOR-I RECEPTOR-ACTIVATED BY A TRANSMEMBRANE MUTATION. TAKAHASHI K (Reprint); YONEZAWA K; NISHIMOTO I. MASSACHUSETTS GEN HOSP EAST, CARDIOVASC RES CTR, BOSTON, MA 02129; HARVARD UNIV, SCH MED, DEPT MED, BOSTON, MA 02129. JOURNAL OF BIOLOGICAL CHEMISTRY (11 AUG 1995) Vol. 270, No. 32, pp. 19041-19045. ISSN: 0021-9258. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We constructed mutant receptors by mutating transmembrane Val(922) of the **human insulin-like growth factor I receptor** (IGF-IR). Assays of receptor kinase and autophosphorylation revealed constitutively augmented tyrosine kinase activity of V922E IGF-IR in both transient and stable expression. The constitutively active tyrosine kinase of this mutant was verified by promoted tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) in the absence of IGF-I. In CHO cells stably expressing V922E IGF-IR, both IRS-1 phosphorylation and the IRS-1-associated phosphoinositide 3-kinase activity were stimulated in the absence of IGF-I to the level attained by 1 nM IGF-I stimulation of wild type IGF-IR, whereas the Ras-mitogen-activated protein kinase pathway was not activated under the same condition. In these CHO cells, V922E IGF-IR significantly stimulated glucose uptake but did not promote mitogenesis in the absence of IGF-I. We thus conclude that the V922E mutation of IGF-IR switches on the intrinsic tyrosine kinase and differentially activates the downstream pathways. This mutant is extremely useful in clarifying the turning on mechanism of IGF-IR as well as the differential roles of individual downstream pathways of receptor tyrosine kinases.

L4 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
1993:641938 Document No. 119:241938 Expression of functional insulin-like growth factor-I receptors by human amnion cells. Kniss, Douglas A.; Zimmerman, Peter D.; Su, Hsing Chih; Hooper, W. Craig; Landon, Mark B.; Gabbe, Steven G. (Coll. Med., Ohio State Univ., Columbus, OH, USA). American Journal of Obstetrics and Gynecology, 169(3), 632-40 (English) 1993. CODEN: AJOGAH. ISSN: 0002-9378.

AB The purpose of the study was to investigate whether amnion cells contain functional insulin-like growth factor-I receptors. To test whether human amnion cells contain insulin-like growth factor-I receptors, radioligand binding studies, affinity crosslinking studies, and Northern blot anal. were conducted in primary amnion cells and in an immortal amnion cell line (WISH). To test whether the insulin-like growth factor-I receptors on amnion cells are functional, cytochalasin B-inhibitable 2-deoxyglucose uptake was measured after stimulating the cells with insulin-like growth factor-I. Radioligand binding studies demonstrated that primary amnion cells and WISH cells contained a single class of high affinity receptors with an apparent dissociation constant of 0.18 ± 0.04 nmol/L and a receptor concentration of 79 ± 26.2 fmol/mg protein and dissociation constant of 0.44 ± 0.03 nmol/L and a receptor concentration of 33.3 ± 6.45 fmol per 106 cells, resp. Affinity crosslinking studies revealed two major insulin-like growth factor-I binding sites, 135 and 270 kd. Both primary amnion cells and WISH cells exhibited cytochalasin B-inhibitable tritiated 2-deoxyglucose uptake in response to insulin-like growth factor-I treatment. Finally, treatment of WISH cells caused tyrosine phosphorylation of three proteins (mol. weight, 116, 95.4, and 83.5 kd) was observed by Western blotting with antiphosphotyrosine **antibodies.** These results provide the first evidence that human amnion epithelial cells contain functional high-affinity insulin-like growth factor-I receptors that mediate glucose transport.

L4 ANSWER 21 OF 33 MEDLINE on STN DUPLICATE 5
94030048. PubMed ID: 8216340. Two new monoclonal **antibodies** against the alpha subunit of the **human insulin-like growth factor-I receptor.** Li S L; Kato J; Paz I B; Kasuya J; Fujita-Yamaguchi Y. (Department of Molecular Genetics, Beckman Research Institute of the City of Hope, Duarte, CA 91010.) Biochemical and biophysical research communications, (1993 Oct 15) 196 (1) 92-8. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Recently, we have reported three monoclonal **antibodies** (mAbs) against purified human placental insulin-like growth factor (IGF)-I receptors. These **antibodies**, in contrast to the well-studied mAb alpha IR-3, stimulate binding of IGF-I and IGF-II to the receptor and DNA synthesis as well [Xiong, et al., Proc. Natl. Acad. Sci. U.S.A. 1992(89), 5356]. Here we describe two additional mAbs, 1H7 and 2C8, against the IGF-I receptor that have characteristics different from either alpha IR-3 or our previously reported mAbs. Both 1H7 and 2C8 bind to the alpha subunit of the IGF-I receptor as determined by immunoblotting. MAb 1H7 inhibited the binding of IGF-I and IGF-II to the IGF-I receptor while 2C8 had no effect on the binding of either ligand to the receptor. When their effects on DNA synthesis were examined using NIH 3T3 cells expressing human IGF-I receptors, 1H7 inhibited basal and IGF-I- or IGF-II-stimulated DNA synthesis whereas 2C8 stimulated basal DNA synthesis but provided no synergism in the presence of IGF-I or IGF-II.

L4 ANSWER 22 OF 33 MEDLINE on STN DUPLICATE 6
92302241. PubMed ID: 1319060. Growth-stimulatory monoclonal **antibodies** against **human insulin-like growth factor I receptor.** Xiong L; Kasuya J; Li S L; Kato J; Fujita-Yamaguchi Y. (Department of Molecular Genetics, Beckman Research Institute of the City of Hope, Duarte, CA 91010.) Proceedings of the National Academy of Sciences of the United States of America, (1992 Jun 15) 89 (12) 5356-60. Journal code: 7505876.

ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Monoclonal **antibodies** (mAbs) against purified human placental insulin-like growth factor I (IGF-I) receptors were prepared and characterized. Three IgG mAbs were specific for the human IGF-I receptor and displayed negligible crossreactivity with the human insulin receptor. They stimulated 125I-labeled IGF-I (125I-IGF-I) or 125I-IGF-II binding to purified human placental IGF-I receptors and to IGF-I receptors expressed in NIH 3T3 cells in contrast to the well-studied mAb alpha IR-3, which inhibits 125I-IGF-I or 125I-IGF-II binding to both forms of IGF-I receptors. The mAbs introduced in this study stimulated DNA synthesis in NIH 3T3 cells expressing human IGF-I receptors approximately 1.5-fold above the basal level and the IGF-I- or IGF-II-stimulated level. In contrast, alpha IR-3 inhibited both basal and IGF-I or IGF-II-stimulated DNA synthesis by approximately 30%. Inhibition of IGF-II-stimulated DNA synthesis by alpha IR-3 was as potent as its inhibition of IGF-I-stimulated DNA synthesis, although IGF-II binding to the IGF-I receptors was not inhibited by IGF-II as potently as was IGF-I. With the purified IGF-I receptors, both inhibitory and stimulatory mAbs were shown to activate autophosphorylation of the IGF-I receptor beta subunit and to induce microaggregation of the receptors. These results suggest that conformational changes resulting from receptor dimerization in the presence of either type of mAb may affect the signal-transducing function of the IGF-I receptor differently. These additional mAbs and alpha IR-3 immunoprecipitated nearly 90% of IGF-I binding activity from Triton X-100-solubilized human placental membranes, indicating that IGF-I receptor reactive with these mAbs is the major form of the IGF-I receptor in human placenta.

L4 ANSWER 23 OF 33 MEDLINE on STN DUPLICATE 7

93055456. PubMed ID: 1430235. **Human insulin-like growth factor I receptor** function in pituitary cells is suppressed by a dominant negative mutant. Prager D; Yamasaki H; Weber M M; Gebremedhin S; Melmed S. (Department of Medicine, Cedars-Sinai Medical Center-UCLA School of Medicine 90048.) Journal of clinical investigation, (1992 Nov) 90 (5) 2117-22. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB Hybrid receptors were studied in GC rat pituitary cells overexpressing either wild-type 950Tyr (WT) human insulin-like growth factor I (IGF-I) receptors or mutant human IGF-I receptors truncated at position 952 in the beta subunit transmembrane region (952STOP). 125I-IGF-I binding was increased in both 950Tyr (WT) (14-fold) and truncated human IGF-I receptor (952STOP) stable transfectants (50-fold), when compared to untransfected cells that contained endogenous rat IGF-I receptors. Metabolic cell labeling followed by immunoprecipitation with monoclonal alpha and beta subunit-specific **antibodies** revealed the presence of hybrid rat/truncated human receptors, truncated transfected human receptors, and WT human IGF-I holotetramers. Both mutant and hybrid receptors were degraded slower than 950Tyr (WT) receptors (> 16 h). Despite their markedly increased ligand binding and prolonged receptor half-life, 952STOP transfectants failed to transduce the IGF-I signal to suppress growth hormone (GH). Also, they neither underwent autophosphorylation nor phosphorylated endogenous proteins. The expected suppression of GH by endogenous rat IGF-I receptors was completely abrogated in 952STOP transfectants ($P < 0.001$ compared to untransfected cells). Mutant 952STOP cells were therefore completely devoid of biological signaling to GH despite the presence of endogenous rat IGF-I receptors. Thus mutant IGF-I receptors block ligand-mediated endogenous rat IGF-I signaling by functioning as a dominant negative forming nonfunctional human/rat hybrid receptors. Defective IGF-I receptors may function therefore as dominant negative phenotypes which suppress normal receptor responses in pituitary cells.

L4 ANSWER 24 OF 33 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1992:48986 Document No.: PREV199293028961; BA93:28961. A REGION OF THE INSULIN RECEPTOR IMPORTANT FOR LIGAND BINDING RESIDUES 450-601 IS RECOGNIZED BY PATIENTS' AUTOIMMUNE **ANTIBODIES** AND INHIBITORY MONOCLONAL **ANTIBODIES.** ZHANG B [Reprint author]; ROTH R A. DEP PHARMACOL, STANFORD UNIV SCH MED, STANFORD, CALIF 94305, USA. Proceedings of the National Academy of Sciences of the United States of America, (1991) Vol. 88, No. 21, pp. 9858-9862.
CODEN: PNASA6. ISSN: 0027-8424. Language: ENGLISH.

AB Chimeric receptors containing different portions of the homologous human insulin receptor, insulin-like growth factor I receptor, and insulin receptor-related receptor were utilized to identify the epitopes recognized by various anti-insulin receptor **antibodies.** The **antibodies** studied included 12 monoclonal **antibodies** to the extracellular domain of the human insulin receptor as well as 15 patients' sera with autoimmune anti-insulin receptor **antibodies.** All of the patients' sera and all 8 monoclonal **antibodies** that inhibit insulin binding were found to recognize an epitope contained within residues 450-601 of the α subunit of the receptor. In contrast, 2 monoclonal **antibodies** that do not inhibit insulin binding were found to recognize the cysteine-rich region of the α subunit. Chimeric insulin receptors that had residues 450-601 replaced with the homologous residues of the insulin-like growth factor I receptor exhibited a decreased ability to bind insulin. In contrast, insulin-like growth factor I receptors that have had the comparable region replaced with that of the insulin receptor showed no decrease in their ability to bind ligand. These results indicate that residues 450-601 of the insulin receptor are important for insulin binding and include the major site for recognition by inhibitory monoclonal **antibodies** and patients' autoimmune anti-receptor **antibodies.**

L4 ANSWER 25 OF 33 MEDLINE on STN DUPLICATE 8

91319003. PubMed ID: 1650422. Radioimmunoassay for **human insulin-like growth factor-I receptor**: applicability to breast carcinoma specimens and cell lines. Pezzino V; Milazzo G; Frittitta L; Vigneri R; Ezaki O; Kasahara M; LeBon T R; Goldfine I D; Fujita-Yamaguchi Y. (Cattedra di Endocrinologia, Universita di Catania, Italy.) Metabolism: clinical and experimental, (1991 Aug) 40 (8) 861-5. Journal code: 0375267. ISSN: 0026-0495. Pub. country: United States. Language: English.

AB A radioimmunoassay for the human insulin-like growth factor-I (IGF-I) receptor was developed using a rabbit polyclonal **antibody** to the human IGF-I receptor and a highly purified IGF-I receptor. The purified receptor was radiolabeled with 125I-Bolton-Hunter reagent. Over 18% of the radiolabeled receptor was immunoprecipitated with the polyclonal antireceptor **antibody.** Purified IGF-I receptor concentrations as low as 5 ng/0.5 mL inhibited the radiolabeled IGF-I receptor binding. Purified insulin receptor weakly inhibited this binding, while the ligand IGF-I did not show inhibition. The radioimmunoassay was applicable to the measurements of IGF-I receptors in the Triton X-100 extracts of various tissues and cells. Breast cancer tissues and cells showed detectable IGF-I receptors, which correlated with IGF-I ligand binding. Receptor content was measurable in placenta and IM-9 cells, but receptor content was not measurable in liver and muscle extracts.

L4 ANSWER 26 OF 33 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1990:515005 Document No.: PREV199090132281; BA90:132281. MONOCLONAL **ANTIBODY** ALPHA-IR-3 INHIBITS THE ABILITY OF INSULIN-LIKE GROWTH FACTOR II TO STIMULATE A SIGNAL FROM THE TYPE I RECEPTOR WITHOUT INHIBITING ITS BINDING. STEELE-PERKINS G [Reprint author]; ROTH R A. DEP PHARMACOL, STANFORD UNIV SCH OF MED, STANFORD, CALIF 94305, USA. Biochemical and Biophysical Research Communications, (1990) Vol. 171, No. 3, pp. 1244-1251.
CODEN: BBRCA9. ISSN: 0006-291X. Language: ENGLISH.

AB We have previously shown that the protein encoded by a human insulin-like

growth factor I (IGF-I) receptor cDNA binds both IGF-I and II with high affinity. In the present studies, we show that a monoclonal **antibody** to the IGF-I receptor, αIR-3, inhibits the binding of IGF-I but not IGF-II to the expressed receptor in intact cells and after solubilization. Surprisingly, this monoclonal **antibody** inhibits the ability of both IGF-I and II to stimulate thymidine synthesis in cells with the expressed receptor. Moreover, this **antibody** inhibits the ability of both IGF-I and II to stimulate the kinase activity of the IGF-I receptor in intact cells. These results indicate that αIR-3 binds to the IGF-I receptor in such a way that it does not inhibit the binding of IGF-II but does inhibit the subsequent ability of the receptor to be activated to transmit a signal.

L4 ANSWER 27 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN

1990:31174 Document No. 112:31174 Insulin-like growth factor-II (IGF-II): a potential autocrine/paracrine growth factor for human breast cancer acting via the IGF-I receptor. Osborne, C. Kent; Coronado, Ester B.; Kitten, Libbey J.; Arteaga, Carlos I.; Fuqua, Suzanne A. W.; Ramasharma, K.; Marshall, Milton; Li, Choh Hao (Health Sci. Cent., Univ. Texas, San Antonio, TX, 78284, USA). Molecular Endocrinology, 3(11), 1701-9 (English) 1989. CODEN: MOENEN. ISSN: 0888-8809.

AB The interaction of insulin-like growth factor-II (IGF-II) with a panel of cultured human breast cancer cell lines, were examined with respect to the possibility that these cells synthesize and secrete IGF-II activity which could have autocrine/paracrine functions. Synthetic IGF-II was mitogenic in 5 of 7 cell lines tested, including the estrogen receptor-pos. lines MCF-7L, ZR75-1, and T47D and the estrogen receptor (ER)-neg. lines Ha578T and MDA-231. IGF-II was slightly less potent than IGF-I in stimulating DNA synthesis in MCF-71 cells, an effect that paralleled its ability to complete for [125I]IGF-I binding in these cells. Affinity labeling studies revealed that IGF-II could also compete for binding to the 130,000 mol. weight α-subunit of the IGF-I receptor. A monoclonal **antibody** to the IGF-I receptor inhibited the mitogenic effects of IGF-II in MCF-7L and MDA-231 cells, suggesting that this receptor mediates the growth effects of IGF-II in these breast cancer cells. Using a RIA and a RRA, IGF-II-like activity was detected in conditioned medium exts. processed to remove IGF-binding proteins from several breast cancer cell lines, with the highest levels found in conditioned medium from MCF-7L and T47D cell lines. IGF-II mRNA transcripts in MCF-7L and T47D cells were identified by Northern blot anal. and were confirmed by RNase protection assay. IGF-II mRNA was increased by estrogen in MCF-7L cells. Apparently, IGF-II is an important mitogen for certain breast cancer cells and its effects are mediated via the IGF-I receptor. The ability of these cells to express IGF-II mRNA and secrete IGF-II activity into the culture medium further supports the hypothesis that IGF-II may have autocrine/paracrine as well as endocrine growth regulatory functions in human breast cancer.

L4 ANSWER 28 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN

1989:434168 Document No. 111:34168 Insulin-like growth factor action and production in adipocytes and endothelial cells from human adipose tissue. Kern, Philip A.; Svoboda, Marjorie E.; Eckel, Robert H.; Van Wyk, Judson J. (Dep. Med., Cedars-Sinai Med. Cent., Los Angeles, CA, 90048, USA). Diabetes, 38(6), 710-17 (English) 1989. CODEN: DIAEAZ. ISSN: 0012-1797.

AB Primary cultures of microvascular endothelial cells and isolated adipocytes were prepared from human omental adipose tissue to study the potentially overlapping roles of insulin and insulin-like growth factors (IGFs) in human adipose tissue. To determine whether adipocytes contain type I IGF receptors, binding expts. were carried out with 125I-labeled IGF-I. At 16°, saturation of specific binding to adipocytes was reached after 30 min and was 0.7%/106 cells. At 37°, chloroquine increased cell-associated 125I-IGF-I, suggesting that IGF-I is internalized and degraded in a manner analogous to insulin. In competition expts., IGF-I competed for binding more effectively than rat IGF-II or insulin. The concns. of IGF-I, rat IGF-II, and insulin necessary to displace 50% of

125I-IGF-I binding were 2.5, 15, and 90 nM, resp. In addition, a monoclonal **antibody** (α-IR3) that has been shown to block the type I IGF receptor was used in competition binding expts. The **antibody** also inhibited binding of 125I-IGF-I to adipocytes. The biol. effects of insulin and IGF-I were examined by studying adipocyte lipoprotein lipase (LPL). Insulin stimulated [14C]glucose incorporation into cellular lipid in a dose-dependent manner, with 50% effective concentration (EC50) of 0.3 nM. However, an increase in LPL activity was observed only at a high insulin concentration, with an EC50 of .apprx.30 nM. In contrast, IGF-I stimulated a progressive increase in LPL, with an EC50 of 3.2 nM. In addition, α-IR3 blocked the stimulatory effect of IGF-I on adipocyte LPL. To study the possible local production of IGFs in adipose tissue, adipose-derived human microvascular endothelial cells were cultured. The conditioned medium from these cells contained significant quantities of immunoreactive IGF. After passing the conditioned medium through a Deltapak C4 100-Å column and eluting with an acetonitrile gradient, IGF was separated from binding protein, and most of the immunoreactive IGF in endothelial cell-conditioned medium consisted of IGF binding protein, with smaller contributions from IGF-II and IGF-I. Thus, in human adipose tissue, IGFs and IGF binding protein are produced by microvascular endothelial cells. In addition, type I IGF receptors are present on adipocytes, and LPL is stimulated through type I receptors.

L4 ANSWER 29 OF 33 MEDLINE on STN DUPLICATE 9

88298804. PubMed ID: 2969892. Expression and characterization of a functional **human insulin-like growth factor I receptor.** Steele-Perkins G; Turner J; Edman J C; Hari J; Pierce S B; Stover C; Rutter W J; Roth R A. (Department of Pharmacology, Stanford University School of Medicine, California 94305-5332.) Journal of biological chemistry, (1988 Aug 15) 263 (23) 11486-92. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Stable transfectants of Chinese hamster ovary (CHO) cells were developed that expressed the protein encoded by a human insulin-like growth factor I (IGF-I) receptor cDNA. The transfected cells expressed approximately 25,000 high affinity receptors for IGF-I (apparent Kd of 1.5 X 10(-9) M), whereas the parental CHO cells expressed only 5,000 receptors per cell (apparent Kd of 1.3 X 10(-9) M). A monoclonal **antibody** specific for the human IGF-I receptor inhibited IGF-I binding to the expressed receptor and immunoprecipitated polypeptides of apparent Mr values approximately 135,000 and 95,000 from metabolically labeled lysates of the transfected cells but not control cells. The expressed receptor was also capable of binding IGF-II with high affinity (Kd approximately 3 nM) and weakly recognized insulin (with about 1% the potency of IGF-I). The human IGF-I receptor expressed in these cells was capable of IGF-I-stimulated autophosphorylation and phosphorylation of endogenous substrates in the intact cell. This receptor also mediated IGF-I-stimulated glucose uptake, glycogen synthesis, and DNA synthesis. The extent of these responses was comparable to the stimulation by insulin of the same biological responses in CHO cells expressing the human insulin receptor. These results indicate that the isolated cDNA encodes a functional IGF-I receptor and that there are no inherent differences in the abilities of the insulin and IGF-I receptors to mediate rapid and long term biological responses when expressed in the same cell type. The high affinity of this receptor for IGF-II also suggests that it may be important in mediating biological responses to IGF-II as well as IGF-I.

L4 ANSWER 30 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN

1988:216950 Document No. 108:216950 Receptor-mediated endocytosis and lysosomal processing of insulin-like growth factor I by mitogenically responsive cells. Furlanetto, Richard W. (Sch. Med., Univ. Pennsylvania, Philadelphia, PA, 19104, USA). Endocrinology, 122(5), 2044-53 (English) 1988. CODEN: ENDOAO. ISSN: 0013-7227.

AB The processing of insulin-like growth factor I (IGF-I) by MG-63, an IGF-I-responsive human osteosarcoma cell line, was investigated. At

37°, the binding of [125I]IGF-I to monolayers of MG-63 cells reaches a maximum after .apprx.1 h and slowly declines thereafter. The addition of the lysosomotropic agents methylamine, chloroquine, and monensin to the binding medium prevents the decline in [125I]IGF-I binding observed in the untreated cells and causes a 1.5-3-fold increase in cell-associated radioactivity after 4 h. Leupeptin, an inhibitor of lysosomal proteases, and colchicine, an inhibitor of endosomal transplant, also increase cell-associated [125I]IGF-I. Thus, the increased radioactivity associated with the treated cells is the result of intracellular accumulation of the ligands and not the result of an increase in cell surface IGF binding. First, no increase in [125I]IGF-I binding is observed in cells preincubated with methylamine at 37° but transferred to 4° (where endocytosis is inhibited) before the addition of the radiolabeled ligands. Second, the increased radioactivity bound by methylamine-treated cells is not removed by washing the cells with dilute acid, a treatment that removes surface-bound [125I]IGF-I. Third, in leupeptin-treated cells [125I]IGF-I accumulates in a subcellular fraction with properties characteristic of lysosomes. Both αIR-3 (100 nM), an **antibody** that specifically inhibits binding to the type I IGF receptor, and high concns. of insulin (900 nM) inhibit the accumulation of [125I]IGF-I by methylamine-treated cells, indicating that internalization of IGF-I occurs through the type I IGF receptor and not through the type II IGF receptor or the IGF-binding protein(s) that is also present on these cells. Evidently, in MG-63 cells IGF-I is endocytosed via the type I IGF receptor and the endocytosed hormone is degraded, at least in part, in lysosomes. These findings are similar to those described for the processing of insulin and other growth factors by their target cells and extend further the homol. between IGF-I and these other agents.

L4 ANSWER 31 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN

1988:564239 Document No. 109:164239 Evidence that receptor aggregation may play a role in transmembrane signaling through the insulin-like growth factor-I receptor. Ikari, Nobuhiko; Yoshino, Hiroko; Moses, Alan C.; Flier, Jeffrey S. (Charles A. Dana Res. Inst., Beth Israel Hosp., Boston, MA, 02215, USA). Molecular Endocrinology, 2(9), 831-7 (English) 1988. CODEN: MOENEN. ISSN: 0888-8809.

AB αIR-3 is a mouse monoclonal **antibody** that binds to an epitope on the human insulin-like growth factor I (IGF-I) receptor and inhibits [125I]IGF-I binding to this receptor on human skin fibroblasts (HSF) and Hep G2 human hepatoblastoma cells. Unlike the natural ligand (IGF-I), neither intact αIR-3 nor its monovalent Fab' fragment stimulate aminoisobutyric acid (AIB) uptake in HSF, and both competitively antagonize IGF-I's ability to produce this effect. However, when HSF are incubated with αIR-3 or its Fab' fragment, subsequent exposure to anti-mouse IgG produces a potent stimulation of AIB uptake. Anti-Mouse IgG by itself does not effect AIB uptake. αIR-3 also antagonizes IGF-I's ability to stimulate glycogen synthesis in Hep G2 cells. As with AIB uptake in HSF, the combination of αIR-3 followed by anti-mouse IgG stimulates glycogen synthesis in Hep G2 cells to the same extent as that produced by IGF-I. The triggering of these 2 biol. effects depends on the concentration of both αIR-3 and anti-mouse IgG. These results are consistent with the possibility that local aggregation or crosslinking of IGF-I receptors plays an important role in transmembrane signaling by this receptor.

L4 ANSWER 32 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN

1988:50016 Document No. 108:50016 Interactions between growth factor receptors and corresponding monoclonal **antibodies** in human tumors. Rodeck, Ulrich; Herlyn, Meenhard; Koprowski, Hilary (Wistar Inst. Anat. Biol., Philadelphia, PA, 19104, USA). Journal of Cellular Biochemistry, 35(4), 315-20 (English) 1987. CODEN: JCEBD5. ISSN: 0730-2312.

AB Monoclonal **antibodies** (MAbs) to the human EGF receptor, the type I insulin-like growth factor (IGF) receptor, and the nerve growth factor

(NGF) receptor were used to study the growth regulation of malignant cells. Anti-EGF receptor MAb 425 inhibited the growth of A 431 squamous carcinoma cells which express high nos. of EGF receptors on their surfaces. Growth inhibition induced by MAb 425 was accompanied by alterations of the cell-cycle distribution of these cells, indicating the ability of a monoclonal **antibody** to act as a biol. active ligand. Growth stimulation of melanoma cells by EGF was unrelated to EGF receptor expression on the cell surface. Insulin- and IGF-I-induced growth stimulation of melanoma cells was inhibited by MAb αIR-3 which reacts with the type I IGF receptor. Apparently, the type I IGF receptor mediated growth stimulation not only by IGF-I but also by insulin. Normal melanocytes and cells of all stages of tumor progression expressed in tissue culture the receptor for NGF, but no effect on the growth of these cells has been observed

L4 ANSWER 33 OF 33 CAPLUS COPYRIGHT 2006 ACS on STN
1986:123828 Document No. 104:123828 Monoclonal **antibody** to the type I insulin-like growth factor (IGF-I) receptor blocks IGF-I receptor-mediated DNA synthesis: clarification of the mitogenic mechanisms of IGF-I and insulin in human skin fibroblasts. Flier, Jeffrey S.; Usher, Patricia; Moses. Alan C. (Harvard Med. Sch., Beth Israel Hosp., Boston, MA, 02215, USA). Proceedings of the National Academy of Sciences of the United States of America, 83(3), 664-8 (English) 1986. CODEN: PNASA6. ISSN: 0027-8424.
AB A monoclonal **antibody** to human placental insulin-like growth factor I (IGF-I) [67763-96-6] receptors (αIR-3), which blocks the binding of IGF-I to placenta and human peripheral blood cells but does not block insulin [9004-10-8] binding under the same conditions, also inhibited the binding of IGF-I (but not insulin) to receptors on human skin fibroblasts. Addnl., αIR-3 antagonized the ability of IGF-I to stimulate DNA formation by fibroblasts; basal DNA formation was unaffected by the **antibody.** Moreover, αIR-3 inhibited the DNA formation response of fibroblasts to insulin but only at concns. which saturated the insulin receptors and at which insulin is probably acting through IGF-I receptors. Thus, insulin acts on both autoreceptors and on IGF-I receptors in its mitogenic effect in human skin fibroblasts.

=> s l1 and (IGF-IR)
L5 620 L1 AND (IGF-IR)

=> s l5 and chimeric
L6 16 L5 AND CHIMERIC

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L7 12 DUP REMOVE L6 (4 DUPLICATES REMOVED)

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L7 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
2005:158698 Document No. 142:259969 Human monoclonal **antibodies** specific to human insulin-like growth factor-1 receptor for treating cancer or hyperproliferative disease. Ludwig, Dale L. (Imclone Systems Incorporated, USA). PCT Int. Appl. WO 2005016970 A2 20050224, 104 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US13852 20040503. PRIORITY: US 2003-2003/PV467177 20030501.
AB This invention relates to human **antibodies** that bind to human

insulin-like growth factor-1 receptor (**IGF-IR**), to derivs. of these **antibodies** (Fabs, single chain **antibodies**, bi-specific **antibodes**, or fusion proteins), and to uses of the **antibodies** and derivs. in therapeutic, and diagnostic methods. The invention relates to nucleic acids encoding the anti-**IGF-IR**, methods of generating the **antibodies** and expression. The invention further relates to combination therapies using ant-**IGF-IR** **antibodies** with anti-neoplastic drugs.

L7 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

2005:1200829 Document No. 143:458527 **Antibodies** to the human insulin-like growth factor I receptor (**IGF-IR**) and/or to insulin/IGF-I hybrid receptors and anticancer and diagnostic uses thereof. Goetsch, Liliane; Corvaia, Nathalie; Duflos, Alain; Haeuw, Jean-Francois; Leger, Olivier; Beck, Alain (Pierre Fabre Medicament, Fr.). U.S. Pat. Appl. Publ. US 2005249730 A1 20051110, 144 pp., Cont.-in-part of U.S. Ser. No. 735,916. (English). CODEN: USXXCO. APPLICATION: US 2004-12353 20041216. PRIORITY: FR 2002-654 20020118; FR 2002-653 20020118; FR 2002-5753 20020507; WO 2003-FR178 20030120; FR 2003-8538 20030711; US 2003-2003/735916 20031216.

AB The present invention relates to novel **antibodies** capable of binding specifically to the human insulin-like growth factor I receptor (**IGF-IR**) and/or the insulin/IGF-I hybrid receptor (hybrid-R) and/or capable of specifically inhibiting the tyrosine kinase activity of said **IGF-IR** and/or hybrid-R, especially monoclonal **antibodies** of murine, **chimeric** and humanized origin, as well as the amino acid and nucleic acid sequences coding for these **antibodies.** Provided are protein and cDNA sequences for anti-**IGF-IR** and/or anti-insulin/IGF-I hybrid receptors **antibodies.** The invention likewise comprises the use of these **antibodies** as a medicament for the prophylactic and/or therapeutic treatment of cancers overexpressing **IGF-IR** and/or hybrid-R or any pathol. connected with the overexpression of said receptor as well as in processes or kits for diagnosis of illnesses connected with the overexpression of the **IGF-IR** and/or hybrid-R. The invention finally comprises products and/or compns. comprising such **antibodies** in combination with anti-EGFR **antibodies** and/or compds. and/or anti-cancer agents or agents conjugated with toxins and their use for the prevention and/or the treatment of certain cancers.

L7 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

2005:346710 Document No. 142:390956 **Antibodies** to insulin-like growth factor I receptor. Goetsch, Liliane; Corvaia, Nathalie; Leger, Olivier; Duflos, Alain; Haeuw, Jean-francois; Beck, Alain (Fr.). U.S. Pat. Appl. Publ. US 2005084906 A1 20050421, 125 pp., Cont.-in-part of Appl. No. PCT/FR03/00178. (English). CODEN: USXXCO. APPLICATION: US 2003-735916 20031216. PRIORITY: FR 2002-654 20020118; FR 2002-653 20020118; FR 2002-5753 20020507; WO 2003-FR178 20030120; FR 2003-8538 20030711.

AB The authors disclose **antibodies** capable of binding specifically to the human insulin-like growth factor I receptor (**IGF-IR**) and/or capable of specifically inhibiting the **IGF-IR** tyrosine kinase activity. The monoclonal **antibodies** are of murine, **chimeric** and humanized origin **antibodies** and can be used as a medicament for the prophylactic and/or therapeutic treatment of cancers overexpressing **IGF-IR** or any pathol. connected with the **IGF-IR** overexpression. Addnl., the authors disclose the use of these **antibodies** in combination with anti-EGFR **antibodies** and/or anti-cancer agents or agents conjugated with toxins and their use for the prevention and/or the treatment of certain cancers.

L7 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

2005:182087 Document No. 142:278741 Single-chain **antibodies** against human insulin-like growth factor I receptor for inhibiting hormone-dependent tumor growth. Fujita-Yamaguchi, Yoko (City of Hope, USA). U.S. Pat. Appl. Publ. US 2005048050 A1 20050303, 19 pp., Cont.-in-part of U.S. Ser. No. 134,519. (English). CODEN: USXXCO. APPLICATION: US 2004-864818 20040610. PRIORITY: US 2000-2000/PV21118U 20000613; US 2000-2000/609776 20000703; US 2002-2002/134519 20020430.

AB A method of inhibiting the growth of hormone-dependent tumor cells in a mammal comprises administering to said mammal an insulin-like growth factor receptor (**IGF-IR**) recombinant **antibody**, wherein said **antibody** can be a single-chain recombinant **antibody**, which can be humanized, capable of blocking agonist interaction with the **IGF-IR**.

L7 ANSWER 5 OF 12 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2005:466382 The Genuine Article (R) Number: 919PU. Insulin-like growth factor-1 controls type 2 T cell-independent B cell response. Baudler S; Baumgartl J; Hampel B; Buch T; Waisman A; Snapper C M; Krone W; Bruning J C (Reprint). Univ Cologne, Inst Genet, Zulpicher Str 47, D-50674 Cologne, Germany (Reprint); Univ Cologne, Inst Genet, D-50674 Cologne, Germany; Univ Cologne, Klin 2, Cologne, Germany; Univ Cologne, Poliklin Innere Med, Cologne, Germany; Ctr Mol Med, Cologne, Germany; Uniformed Serv Univ Hlth Sci, Dept Pathol, Bethesda, MD 20814 USA. jens.bruening@uni-koeln.de. JOURNAL OF IMMUNOLOGY (1 MAY 2005) Vol. 174, No. 9, pp. 5516-5525. ISSN: 0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The IGF-1 receptor (**IGF-IR**) is expressed on T and B lymphocytes, and the expression of the insulin- and IGF-1-signaling machinery undergoes defined changes throughout lineage differentiation, offering a putative role for IGF-1 in the regulation of immune responses. To study the role of the **IGF-IR** in lymphocyte differentiation and function in vivo, we have reconstituted immunodeficient RAG2-deficient mice with IGF-1R(-/-) fetal liver cells. Despite the absence of IGF-1Rs, the development and ex vivo activation of B and T lymphocytes were unaltered in these **chimeric** mice. By contrast, the humoral immune response to the T cell-independent type 2 Ag 4-hydroxy-3-nitrophenyl acetyl-Ficoll was significantly reduced in mice reconstituted with IGF-1R-deficient fetal liver cells, whereas responses to the T cell-dependent Ag 4-hydroxy-3-nitrophenyl acetyl-chicken globulin were normal. Moreover, in an in vitro model of T cell-independent type 2 responses, IGF-1 promoted Ig production potently upon polyvalent membrane-IgD cross-linking. These data indicate that functional JGF-1R signaling is required for T cell-independent B cell responses in vivo, defining a novel regulatory mechanism for the immune response against bacterial polysaccharides.

L7 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

2004:799597 Document No. 141:312944 Phagemid library-derived human anti-**IGF-IR** scFv **antibodies** for diagnosis and treatment of cancers. Morton, Philip A.; Arbuckle, J. Alan; Bailey, Karen J.; Nicastro, Peter J.; Runnels, Herbert A. (Pharmacia Corporation, USA). PCT Int. Appl. WO 2004083248 A1 20040930, 259 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-IB646 20040304. PRIORITY: US 2003-2003/PV455094 20030314.

AB Human, **chimeric**, humanized, bispecific **antibodies** and fragments specific for insulin-like growth factor I receptor (**IGF**

-**IR**) are provided. The **antibodies** and fragments thereof may block binding of IGF-I or IGF-II to **IGF-IR** . Antagonist **antibodies** can be employed to block binding of IGF-I to **IGF-IR** or substantially inhibit **IGF** -**IR** activation. The **IGF-IR** **antibodies** may be included in pharmaceutical compns., articles of manufacture, or kits. Methods of treating cancer, inflammation, and pathol. liver conditions, using the **IGF-IR antibodies** are also provided.

L7 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
2003:571020 Document No. 139:132446 Monoclonal and humanized **antibodies** to insulin-like growth factor 1 receptors for use in the diagnosis and treatment of disease. Goetsch, Liliane; Corvaia, Nathalie; Leger, Olivier (Pierre Fabre Medicament, Fr.). PCT Int. Appl. WO 2003059951 A2 20030724, 164 pp. DESIGNATED STATES: W: AU, CA, CN, JP, MX, US, ZA; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (French). CODEN: PIXXD2. APPLICATION: WO 2003-FR178 20030120. PRIORITY: US 2002-2002/200653 20020118; US 2002-2002/200654 20020118; US 2002-2002/205753 20020507.
AB The invention relates to novel **antibodies** capable of binding specifically to the human Insulin-like Growth Factor-I Receptor (**IGF-IR**), in particular monoclonal of murine origin, **chimeric** and humanized as well as the amino and nucleic acid sequences coding for said **antibodies.** The invention also concerns the use of said **antibodies** as medicine for prophylactic and/or therapeutic treatments of cancers as well as methods or kit for diagnosis of diseases related to overexpression of the **IGF-IR** receptor. The invention further concerns products and/or compns. containing such **antibodies** combined with **antibodies** to epidermal growth factor receptors and/or compds. and/or anti-cancer agents or conjugates with toxins and their use for preventing and/or treating certain cancers.

L7 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
2003:573239 Document No. 139:132447 Monoclonal and humanized **antibodies** to insulin-like growth factor 1 receptors for use in diagnosis and treatment of cancer. Goetsch, Liliane; Leger, Olivier; Corvaia, Nathalie (Pierre Fabre Medicament, Fr.). Fr. Demande FR 2834990 A1 20030725, 137 pp. (French). CODEN: FRXXBL. APPLICATION: FR 2002-653 20020118.
AB The invention relates to novel **antibodies** capable of binding specifically to the human Insulin-like Growth Factor-I Receptor (**IGF-IR**), in particular monoclonal of murine origin, **chimeric** and humanized as well as the amino and nucleic acid sequences coding for said **antibodies.** The invention also concerns the use of said **antibodies** as medicine for prophylactic and/or therapeutic treatments of cancers as well as methods or kit for diagnosis of diseases related to overexpression of the **IGF-IR** receptor. The invention further concerns products and/or compns. containing such **antibodies** combined with **antibodies** to epidermal growth factor receptors and/or compds. and/or anti-cancer agents or conjugates with toxins and their use for preventing and/or treating certain cancers.

L7 ANSWER 9 OF 12 MEDLINE on STN DUPLICATE 1
2004012514. PubMed ID: 14710366. Combined effects of tamoxifen and a **chimeric** humanized single chain **antibody** against the type I IGF receptor on breast tumor growth in vivo. Ye J-J; Liang S-J; Guo N; Li S-L; Wu A M; Giannini S; Sachdev D; Yee D; Brunner N; Ikle D; Fujita-Yamaguchi Y. (Department of Molecular Biology, Beckman Research Institute of the City of Hope, Duarte, CA 91010, USA.) Hormone and metabolic research. Hormon- und Stoffwechselforschung. Hormones et metabolisme, (2003 Nov-Dec) 35 (11-12) 836-42. Journal code: 0177722. ISSN: 0018-5043. Pub. country: Germany: Germany, Federal Republic of.

Language: English.

AB Proliferative and anti-apoptotic actions of IGFs are mediated by the IGF-I receptor (**IGF-IR**), to which both IGF-I and -II bind with high affinity. We previously reported that alphaIGF-IR scFv-Fc (scFv-Fc) consisting of the alphaIGF-IR scFv and human IgG (1) Fc domain retained general characteristics of the parental 1H7 monoclonal **antibody**, and significantly suppressed MCF-7 tumor growth. We proposed **IGF-IR** down-regulation as a possible mechanism for inhibition of MCF-7 tumor growth. To further determine the therapeutic potentials of this approach, in vivo effects of this **antibody** on breast tumor growth were evaluated in the absence or presence of tamoxifen (Tam) using a T61 human breast tumor model. T61 xenograft growth in athymic mice was compared under five conditions, PBS, scFv-Fc, Tam, scFv-Fc+Tam, and control **antibody.** While treatment with PBS and control **antibody** did not affect T61 tumor growth, scFv-Fc, Tam, and scFv-Fc+Tam treatments significantly suppressed the tumor growth during the first two weeks of treatment. Although the growth inhibitory effect of scFv-Fc during the first two weeks was significant, the tumor grew as rapidly as PBS-treated tumors thereafter. This rapid tumor growth was suppressed when scFv-Fc was combined with Tam. Throughout four weeks, the combined Tam+scFv-Fc treatment was more effective in inhibiting the T61 tumor growth than scFv-Fc or Tam treatment alone. scFv-Fc treatment down-regulated **IGF-IR** which appears to contribute to tumor growth inhibition. This study provides evidence that simultaneous targeting of **IGF-IR** and the estrogen receptor may enhance the therapeutic effect.

L7 ANSWER 10 OF 12 MEDLINE on STN

2000425856. PubMed ID: 10961344. Structure and function of the type 1 insulin-like growth factor receptor. Adams T E; Epa V C; Garrett T P; Ward C W. (CSIRO Health Sciences and Nutrition, Parkville, Victoria, Australia.. Tim.Adams@hsn.csiro.au) . Cellular and molecular life sciences : CMLS, (2000 Jul) 57 (7) 1050-93. Ref: 388. Journal code: 9705402. ISSN: 1420-682X. Pub. country: Switzerland. Language: English.

AB The type 1 insulin-like growth factor receptor (IGF-1R), a transmembrane tyrosine kinase, is widely expressed across many cell types in foetal and postnatal tissues. Activation of the receptor following binding of the secreted growth factor ligands IGF-1 and IGF-2 elicits a repertoire of cellular responses including proliferation, and the protection of cells from programmed cell death or apoptosis. As a result, signalling through the IGF-1R is the principal pathway responsible for somatic growth in foetal mammals, whereas somatic growth in postnatal animals is achieved through the synergistic interaction of growth hormone and the IGFs. Forced overexpression of the IGF-1R results in the malignant transformation of cultured cells: conversely, downregulation of IGF-1R levels can reverse the transformed phenotype of tumour cells, and may render them sensitive to apoptosis in vivo. Elevated levels of **IGF-IR** are observed in a variety of human tumour types, whereas epidemiological studies implicate the IGF-1 axis as a predisposing factor in the pathogenesis of human breast and prostate cancer. The IGF-1R has thus emerged as a therapeutic target for the development of antitumour agents. Recent progress towards the elucidation of the three-dimensional structure of the extracellular domain of the IGF-1R represents an opportunity for the rational assembly of small molecule antagonists of receptor function for clinical use.

L7 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

2000:598547 Document No. 134:177022 Single-chain **antibodies** against human insulin-like growth factor I receptor: expression, purification, and effect on tumor growth. Li, Shu-Lian; Liang, Shu-Jian; Guo, Ning; Wu, Anna M.; Fujita-Yamaguchi, Yoko (Department of Molecular Biology, Beckman Research Institute of the City of Hope, Duarte, CA, 91010, USA). Cancer Immunology Immunotherapy, 49(4-5), 243-252 (English) 2000. CODEN: CIIMDN. ISSN: 0340-7004. Publisher: Springer-Verlag.

AB Insulin-like growth factors (IGF) I and II are potent mitogens for a

variety of cancer cells. The proliferative and anti-apoptotic actions of IGF are mediated by the IGF-I receptor (**IGF-IR**), to which both IGF-I and IGF-II bind with high affinity. To investigate the mitogenic and anti-apoptotic activities of **IGF-IR** and to achieve better inhibition of **IGF-IR** function, single-chain **antibodies** against human **IGF-IR** (.alpha.**IGF-IR** scFvs) were constructed and expressed. IgG cDNA encoding variable regions of light and heavy chains (VL and VH) from mouse IgG were cloned from a hybridoma producing the 1H7 α **IGF-IR** monoclonal **antibody.** The splice-overlap extension polymerase chain reaction was used to assemble a gene encoding the .alpha.**IGF-IR** scFv, including the N-terminal signal peptide, VL, linker peptide, VH, and C-terminal DYKD tag. Two types of soluble .alpha.**IGF-IR** scFvs, a prototype .alpha.**IGF-IR** scFv and its alternative type .alpha.**IGF-IR** scFv-Fc, were constructed and expressed in murine myeloma cells. .alpha.**IGF-IR** scFv-Fc, containing the human IgG1 Fc domain, was stably expressed in NS0 myeloma cells, using a glutamine synthase selection system, and purified from the conditioned medium of stable clones by protein-A-agarose chromatog. Levels of .alpha.**IGF-IR** scFv-Fc expression ranged from 40 mg/l to 100 mg/l conditioned medium. SDS-PAGE anal. under reducing and nonreducing conditions indicated that .alpha.**IGF-IR** scFv-Fc is a dimeric **antibody.** .alpha.**IGF-IR** scFv-Fc retained general characteristics of the parental 1H7 monoclonal **antibody** except that its binding affinity for **IGF-IR** was estimated to be approx. 108 M-1, which was one-order of magnitude lower than that of 1H7 monoclonal **antibody.** Injection of .alpha.**IGF-IR** scFv-Fc (500 μg/mouse, twice a week) significantly suppressed MCF-7 tumor growth in athymic mice. These results suggest that the .alpha.**IGF-IR** scFv-Fc is a first-generation recombinant .alpha.**IGF-IR** for the potential development of future .alpha.**IGF-IR** therapeutics.

L7 ANSWER 12 OF 12 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1991:309181 The Genuine Article (R) Number: FN552. BINDING-PROPERTIES OF **CHIMERIC** INSULIN-RECEPTORS CONTAINING THE CYSTEINE-RICH DOMAIN OF EITHER THE INSULIN-LIKE GROWTH FACTOR-I RECEPTOR OR THE INSULIN-RECEPTOR RELATED RECEPTOR. ZHANG B (Reprint); ROTH R A. STANFORD UNIV, MED CTR, SCH MED, DEPT PHARMACOL, STANFORD, CA 94305. BIOCHEMISTRY (28 MAY 1991) Vol. 30, No. 21, pp. 5113-5117. ISSN: 0006-2960. Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB We constructed and expressed **chimeric** receptor cDNAs with insulin receptor exon 3 (residues 191-297 of the cysteine-rich region) replaced with either the comparable region of the insulin-like growth factor I receptor (**IGF-IR**) or the insulin receptor related receptor (IRR). Both **chimeric** receptors still could bind insulin with as high affinity as the wild-type receptor. In addition, **chimeric** receptors containing exon 3 of the **IGF-IR** could also bind with high affinity both IGF-I and IGF-II. In contrast, **chimeric** receptors containing exon 3 of IRR did not bind either IGF-I, IGF-II, or relaxin. These results indicate that (1) the high affinity of binding of insulin to its receptor can occur in the absence of insulin receptor specific residues encoded by exon 3, the cysteine-rich region; (2) the cysteine-rich region of the IGF-I receptor can confer high-affinity binding to both IGF-I and IGF-II; and (3) the IRR is unlikely to be a receptor for either IGF-I, IGF-II, or relaxin.

=> s l5 and bispecific
L8 4 L5 AND BISPECIFIC

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L9 4 DUP REMOVE L8 (0 DUPLICATES REMOVED)

=> d l9 1-4 cbib abs

L9 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
2005:346710 Document No. 142:390956 **Antibodies** to insulin-like growth factor I receptor. Goetsch, Liliane; Corvaia, Nathalie; Leger, Olivier; Duflos, Alain; Haeuw, Jean-francois; Beck, Alain (Fr.). U.S. Pat. Appl. Publ. US 2005084906 A1 20050421, 125 pp., Cont.-in-part of Appl. No. PCT/FR03/00178. (English). CODEN: USXXCO. APPLICATION: US 2003-735916 20031216. PRIORITY: FR 2002-654 20020118; FR 2002-653 20020118; FR 2002-5753 20020507; WO 2003-FR178 20030120; FR 2003-8538 20030711.
AB The authors disclose **antibodies** capable of binding specifically to the human insulin-like growth factor I receptor (**IGF-IR**) and/or capable of specifically inhibiting the **IGF-IR** tyrosine kinase activity. The monoclonal **antibodies** are of murine, chimeric and humanized origin **antibodies** and can be used as a medicament for the prophylactic and/or therapeutic treatment of cancers overexpressing **IGF-IR** or any pathol. connected with the **IGF-IR** overexpression. Addnl., the authors disclose the use of these **antibodies** in combination with anti-EGFR **antibodies** and/or anti-cancer agents or agents conjugated with toxins and their use for the prevention and/or the treatment of certain cancers.

L9 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
2004:799597 Document No. 141:312944 Phagemid library-derived human anti-**IGF-IR** scFv **antibodies** for diagnosis and treatment of cancers. Morton, Philip A.; Arbuckle, J. Alan; Bailey, Karen J.; Nicastro, Peter J.; Runnels, Herbert A. (Pharmacia Corporation, USA). PCT Int. Appl. WO 2004083248 A1 20040930, 259 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-IB646 20040304. PRIORITY: US 2003-2003/PV455094 20030314.
AB Human, chimeric, humanized, **bispecific antibodies** and fragments specific for insulin-like growth factor I receptor (**IGF-IR**) are provided. The **antibodies** and fragments thereof may block binding of IGF-I or IGF-II to **IGF-IR**. Antagonist **antibodies** can be employed to block binding of IGF-I to **IGF-IR** or substantially inhibit **IGF-IR** activation. The **IGF-IR** **antibodies** may be included in pharmaceutical compns., articles of manufacture, or kits. Methods of treating cancer, inflammation, and pathol. liver conditions, using the **IGF-IR antibodies** are also provided.

L9 ANSWER 3 OF 4 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
2004189930 EMBASE Anti-Insulin-Like Growth Factor Strategies in Breast Cancer. Jerome L.; Shiry L.; Leyland-Jones B.. Dr. B. Leyland-Jones, Department of Oncology, McGill University, 546 Pine Ave West, Montreal, Que. H2W 1S6, Canada. Seminars in Oncology Vol. 31, No. 1 SUPPL. 3, pp. 54-63 2004.
Refs: 102.
ISSN: 0093-7754. CODEN: SOLGAV

Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 20040528
AB The insulin-like growth factors (IGF-I and -II) are potent mitogens and survival factors for both normal and malignant breast cells. These effects are mediated primarily through the IGF-I receptor (**IGF-IR**), which is significantly overexpressed and highly activated in breast tumors. The IGF-binding proteins are competitive inhibitors of IGF/**IGF-IR** interaction, limiting cellular proliferation and survival. Higher serum IGF-I levels or an increased ratio of IGF-I to IGF binding protein-3 is associated with an increased risk of developing breast cancer. Hence, interest in the IGF system as a potential target for the development of novel antineoplastic therapies has ensued. Several strategies to interrupt **IGF-IR** signaling are currently being evaluated for the treatment of breast cancer, including suppression of IGF production, reduction of functional **IGF-IR** levels, neutralization of IGF action, and inhibition of **IGF-IR** activation.

L9 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
2002:521793 Document No. 137:77889 Human **antibodies** to insulin-like growth factor I receptor. Cohen, Bruce D.; Beebe, Jean; Miller, Penelope E.; Moyer, James D.; Corvalan, Jose R.; Gallo, Michael (Pfizer Inc., USA; Abgenix, Inc.). PCT Int. Appl. WO 2002053596 A2 20020711, 172 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US51113 20011220. PRIORITY: US 2001-2001/PV259927 20010105.
AB The authors disclose the preparation and characterization of **antibodies** that specifically bind to human insulin-like growth factor I receptor (**IGF-IR**). The **antibodies** were prepared by immunization of XenoMouse with either the extracellular domain of human **IGF-IR** or with cells transformed for surface expression of the receptor. The isolated **antibodies** were shown to down-regulate **IGF-IR**, to prevent its phosphorylation induced by ligand, and to exhibit tumor growth inhibitory activities either alone or in combination with chemotherapeutic agents.

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=> s anti-IGF-IR
L10        145 ANTI-IGF-IR

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L11         43 DUP REMOVE L10 (102 DUPLICATES REMOVED)

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L12          1 L11 AND "7C10"

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L12 ANSWER 1 OF 1     MEDLINE on STN
2004574411.    PubMed ID: 15386423.   A recombinant humanized anti-insulin-like growth factor receptor type I antibody (h7C10) enhances the antitumor activity of vinorelbine and anti-epidermal growth factor receptor therapy against human cancer xenografts. Goetsch Liliane; Gonzalez Alexandra; Leger Olivier; Beck Alain; Pauwels Petrus J; Haeuw Jean Francois; Corvaia Nathalie. (Centre d'Immunologie Pierre Fabre, 5 Avenue Napoleon III, 74160, St. Julien en Genevois, France.. Liliane.Goetsch@pierre-fabre.com)
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. International journal of cancer. Journal international du cancer, (2005 Jan 10) 113 (2) 316-28. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB Interaction of insulin-like growth factor receptor I (IGF-IR) with its ligands has been reported to induce cell proliferation, transformation and blockade of cell apoptotic functions. IGF-IR is overexpressed on numerous tumor cell types and its blockade could be of importance for anti-cancer therapy. We have generated a humanized **anti-IGF-IR** antibody h7C10 that blocks in vitro IGF-I and IGF-II-induced cell proliferation of MCF-7 breast cancer cells. Analysis of the IGF-I transduction cascade demonstrated that the humanized **anti-IGF-IR** antibody and its murine parental form block IGF-I-induced tyrosine phosphorylation, both its beta-chain and IRS-1 tyrosine phosphorylation. This presumably leads to cell cycle arrest and, consequently, growth inhibition. Treatment of nude mice bearing either human breast cancer cells (MCF-7) or non small lung cancer cells (A549) with h7C10, or its murine parental form **7C10**, inhibited significantly tumor growth. An almost complete inhibition of A549 tumor growth was observed when mice were treated with the **anti-IGF-IR** antibody combined with either a chemotherapeutic agent, Vinorelbine or an anti-epidermal growth factor receptor (EGFR) antibody, 225. Combined therapy prolonged significantly the life span of mice in an orthotopic in vivo model of A549; the combination of the **anti-IGF-IR** antibody with an anti-EGFR antibody was superior to the Vinorelbine combination. The present results indicate that the humanized **anti-IGF-IR** antibody h7C10 has a great potential for cancer therapy when combined with either a chemotherapeutic agent or an antibody that targets other growth factor receptors, such as the epidermal growth factor receptor.

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L11 ANSWER 1 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN

2005:347038 Document No. 142:409720 Anti-Mystique protein antibodies and IGF-I responsive Mystique genes and RNAs for drug screening, diagnosis and therapy of cancer and metastasis. O'Connor, Rosemary; Loughran, Gary (University College Cork-National University of Ireland, Cork, Ire.). PCT Int. Appl. WO 2005035561 A1 20050421, 59 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-IE141 20041014. PRIORITY: US 2003-2003/PV510148 20031014.

AB Disclosed are novel PDZ-LIM domain-containing proteins, i.e. Mystique 1-5 proteins encoded by IGF-I responsive Mystique genes having nucleic acid sequence SEQ ID Number 1, 2, 3, 4, 5, 6 or a derivative or mutant or fragment or variant or peptide thereof. The human and mouse proteins promote the attachment and modulates the motility and invasion capability of cells. Monoclonal and polyclonal antibodies and antisera specific to these Mystique proteins as well as RNA oligonucleotides and DNA fragments are useful for diagnosis and therapy of cancer, metastasis, wound, inflammation, autoimmune disease, AIDS, and cell death caused by radiotherapy, chemotherapy or acute hypoxic injury. The invention also includes method of screening compds. for use in **anti-IGF-IR** therapy and as antitumor agents.

L11 ANSWER 2 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN

2005:158698 Document No. 142:259969 Human monoclonal antibodies specific to human insulin-like growth factor-1 receptor for treating cancer or

hyperproliferative disease. Ludwig, Dale L. (Imclone Systems Incorporated, USA). PCT Int. Appl. WO 2005016970 A2 20050224, 104 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US13852 20040503. PRIORITY: US 2003-2003/PV467177 20030501.

AB This invention relates to human antibodies that bind to human insulin-like growth factor-1 receptor (IGF-IR), to derivs. of these antibodies (Fabs, single chain antibodies, bi-specific antibodes, or fusion proteins), and to uses of the antibodies and derivs. in therapeutic, and diagnostic methods. The invention relates to nucleic acids encoding the **anti -IGF-IR**, methods of generating the antibodies and expression. The invention further relates to combination therapies using ant-IGF-IR antibodies with anti-neoplastic drugs.

L11 ANSWER 3 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN

2005:1200829 Document No. 143:458527 Antibodies to the human insulin-like growth factor I receptor (IGF-IR) and/or to insulin/IGF-I hybrid receptors and anticancer and diagnostic uses thereof. Goetsch, Liliane; Corvaia, Nathalie; Duflos, Alain; Haeuw, Jean-Francois; Leger, Olivier; Beck, Alain (Pierre Fabre Medicament, Fr.). U.S. Pat. Appl. Publ. US 2005249730 A1 20051110, 144 pp., Cont.-in-part of U.S. Ser. No. 735,916. (English). CODEN: USXXCO. APPLICATION: US 2004-12353 20041216. PRIORITY: FR 2002-654 20020118; FR 2002-653 20020118; FR 2002-5753 20020507; WO 2003-FR178 20030120; FR 2003-8538 20030711; US 2003-2003/735916 20031216.

AB The present invention relates to novel antibodies capable of binding specifically to the human insulin-like growth factor I receptor (IGF-IR) and/or the insulin/IGF-I hybrid receptor (hybrid-R) and/or capable of specifically inhibiting the tyrosine kinase activity of said IGF-IR and/or hybrid-R, especially monoclonal antibodies of murine, chimeric and humanized origin, as well as the amino acid and nucleic acid sequences coding for these antibodies. Provided are protein and cDNA sequences for **anti-IGF-IR** and/or anti-insulin/IGF-I hybrid receptors antibodies. The invention likewise comprises the use of these antibodies as a medicament for the prophylactic and/or therapeutic treatment of cancers overexpressing IGF-IR and/or hybrid-R or any pathol. connected with the overexpression of said receptor as well as in processes or kits for diagnosis of illnesses connected with the overexpression of the IGF-IR and/or hybrid-R. The invention finally comprises products and/or compns. comprising such antibodies in combination with anti-EGFR antibodies and/or compds. and/or anti-cancer agents or agents conjugated with toxins and their use for the prevention and/or the treatment of certain cancers.

L11 ANSWER 4 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN

2005:346710 Document No. 142:390956 Antibodies to insulin-like growth factor I receptor. Goetsch, Liliane; Corvaia, Nathalie; Leger, Olivier; Duflos, Alain; Haeuw, Jean-francois; Beck, Alain (Fr.). U.S. Pat. Appl. Publ. US 2005084906 A1 20050421, 125 pp., Cont.-in-part of Appl. No. PCT/FR03/00178. (English). CODEN: USXXCO. APPLICATION: US 2003-735916 20031216. PRIORITY: FR 2002-654 20020118; FR 2002-653 20020118; FR 2002-5753 20020507; WO 2003-FR178 20030120; FR 2003-8538 20030711.

AB The authors disclose antibodies capable of binding specifically to the human insulin-like growth factor I receptor (IGF-IR) and/or capable of specifically inhibiting the IGF-IR tyrosine kinase activity. The monoclonal antibodies are of murine, chimeric and humanized origin antibodies and can be used as a medicament for the prophylactic and/or therapeutic treatment of cancers overexpressing IGF-IR or any pathol. connected with the IGF-IR overexpression. Addnl., the authors disclose the use of these antibodies in combination with anti-EGFR antibodies

and/or anti-cancer agents or agents conjugated with toxins and their use for the prevention and/or the treatment of certain cancers.

L11 ANSWER 5 OF 43 MEDLINE on STN DUPLICATE 1
2005640236. PubMed ID: 16322262. Insulin-like growth factor-I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. Nahta Rita; Yuan Linda X H; Zhang Bing; Kobayashi Ryuji; Esteva Francisco J. (Department of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030-4009, USA.) Cancer research, (2005 Dec 1) 65 (23) 11118-28. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The majority of breast cancer patients who achieve an initial therapeutic response to the human epidermal growth factor receptor 2 (HER-2)-targeted antibody trastuzumab will show disease progression within 1 year. We previously reported the characterization of SKBR3-derived trastuzumab-resistant pools. In the current study, we show that HER-2 interacts with insulin-like growth factor-I receptor (IGF-IR) uniquely in these resistant cells and not in the parental trastuzumab-sensitive cells. The occurrence of cross talk between IGF-IR and HER-2 exclusively in resistant cells is evidenced by the IGF-I stimulation resulting in increased phosphorylation of HER-2 in resistant cells, but not in parental cells, and by the inhibition of IGF-IR tyrosine kinase activity leading to decreased HER-2 phosphorylation only in resistant cells. In addition, inhibition of IGF-IR tyrosine kinase activity by I-OMe-AG538 increased sensitivity of resistant cells to trastuzumab. HER-2/IGF-IR interaction was disrupted on exposure of resistant cells to the **anti-IGF-IR** antibody alpha-IR3 and, to a lesser extent, when exposed to the anti-HER-2 antibody pertuzumab. Heterodimer disruption by alpha-IR3 dramatically restored sensitivity to trastuzumab and resistant cells showed a slightly increased sensitivity to pertuzumab versus parental cells. Neither alpha-IR3 nor pertuzumab decreased HER-2 phosphorylation, suggesting that additional sources of phosphorylation other than IGF-IR exist when HER-2 and IGF-IR are not physically bound. Our data support a unique interaction between HER-2 and IGF-IR in trastuzumab-resistant cells such that cross talk occurs between IGF-IR and HER-2. These data suggest that the IGF-IR/HER-2 heterodimer contributes to trastuzumab resistance and justify the need for further studies examining this complex as a potential therapeutic target in breast cancers that have progressed while on trastuzumab.

L11 ANSWER 6 OF 43 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2006:44771 Document No.: PREV200600053972. IGF-1 activates EGF receptor in human corneal epithellal cells. Lee, K.-S. [Reprint Author]; Lyu, J.; Joo, C.-K.. IOVS, (2005) Vol. 46, No. Suppl. S, pp. 2116.
Meeting Info.: Annual Meeting of the Association-for-Research-in-Vision-and-Ophthalmology. Ft Lauderdale, FL, USA. May 01 -05, 2005. Assoc Res Vis & Ophthalmol.
CODEN: IOVSDA. ISSN: 0146-0404. Language: English.

AB Purpose: Wound healing requires a complex processes to cover defect area and quickly re-establish the barrier function of the injury. These include the proliferation slid migration of epithelial cells. The several growth factors involved in corneal wound healing. Insulin-like, growth factor 1 (IGF-1) of these factors has been known as a stimulator the proliferation and migration of epithelial cells to coverage the defected area. However, the cellular mechanism that regulates the separated process is unclear.Methods: To investigate the cellular responses for IGF-1 in corneal epithelialeel Is. we tested the proliferation and migration using the SV40 transformed cells (HCET). HECT cells (4X10(2)) were sced, incubated for 24 hrs inserum free-medium, and treated with IGF-1. The rate of growth was determined by using the Proliferation Reagent WST-1. The migration assays were performed by the 8 mm-pore, Tissue Culture Inserts. HCET were treated with IGF-1(50ng/ml) or EGF(25ng/ml), with a neutralizing antibody to anti-EGFR or **anti-IGF-IR** toestablish the intracellular mechanism. Western

blotting was then subjected with antibodies to anti-phospho-ERK and anti-phospho-Akt.Results: ERK and AKT were rapidly activated by IGF-1. Interestingly, the activation of ERK was reduced by the inhibition of EGFR, but not by the inhibition of IGF-IR. In contrast, Akt activation was not changed by their inhibition. HCET cells treated with IGF-1 revealed the increased proliferation and migrationrate compared with control cells. However, the proliferation and migration caused by IGF-1 showed the different signal pathways. The growth rate of the HCET cells incubated with IGF-1 and a neutralizing antibody to anti-EGFR was decreased compared with cells incubated with IGF-1 and IgG. The migration of HCET cells was regulated by the IGF-1R, rather than EFGR.Conclusions: In this study, we found that IGF activates both IGF-1R and EGFR in corneal epithelial cells, and that IGF can promote the compartmentalized responses through different pathway during wound healing. Our finding provides, to our knowledge, for the first time die dual function of IGF in corneal epithelia] cells.

L11 ANSWER 7 OF 43 MEDLINE on STN DUPLICATE 2
2005593042. PubMed ID: 16273217. The molecular mechanisms responsible for resistance to ET-743 (Trabectidin; Yondelis) in the Ewing's sarcoma cell line, TC-71. Manara M C; Perdichizzi S; Serra M; Pierini R; Benini S; Hattinger C M; Astolfi A; Bagnati R; D'Incalci M; Picci P; Scotlandi K. (Laboratorio di Ricerca Oncologica, Istituti Ortopedici Rizzoli, I-40136 Bologna, Italy.) International journal of oncology, (2005 Dec) 27 (6) 1605-16. Journal code: 9306042. ISSN: 1019-6439. Pub. country: Greece. Language: English.
AB Identification of new active agents against sarcoma is considered an important challenge in medical oncology. ET-743 (Trabectidin; Yondelis) has recently emerged as the first active drug developed against sarcoma in the last two decades, with promising results especially against soft-tissue sarcoma and Ewing's sarcoma (ES). In this study, we analyzed the molecular mechanisms responsible for resistance to ET-743 in ES cells. Three resistant cell variants (TC/ET 3 nM, TC/ET 6 nM and TC/ET 12 nM) were obtained, showing 28-, 47- and 102-fold increase in ET-743 resistance. Cross-resistance to other drugs was analyzed. Comparative genomic hybridization and cDNA microarray technology were employed to characterize and compare the gene expression profile of two TC/ET variants with the parental cell line. TC/ET cells show a conventional multidrug resistance phenotype and P-glycoprotein overexpression was found to significantly contribute to ET-743 resistance. However, functional studies with the cyclosporine analogue, PSC-833, indicate that other mechanisms are involved in resistance to ET-743. The gene expression profile of TC/ET cells indicated, among up-regulated genes, an increase in expression of insulin-like growth factor receptor-I (IGF-IR) and one of its major intracellular mediators, insulin receptor substrate-1. Functional studies using a neutralizing antibody **anti-IGF-IR** confirmed involvement of this signaling pathway in resistance to ET-743. Simultaneous blockage of both P-glycoprotein and IGF-IR completely restored sensitivity to ET-743 in ES cells. Overall, these findings provide impetus for future studies testing the therapeutic value of new specific inhibitors of P-glycoprotein and IGF-IR, which could represent a concrete therapeutic option for ES patients refractory to conventional agents.

L11 ANSWER 8 OF 43 MEDLINE on STN DUPLICATE 3
2005293486. PubMed ID: 15913990. Prognostic and therapeutic relevance of HER2 expression in osteosarcoma and Ewing's sarcoma. Scotlandi Katia; Manara Maria C; Hattinger Claudia M; Benini Stefania; Perdichizzi Stefania; Pasello Michela; Bacci Gaetano; Zanella Licciana; Bertoni Franco; Picci Piero; Serra Massimo. (Laboratorio di Ricerca Oncologica, Istituti Ortopedici Rizzoli, Via di Barbiano 1/10, 40136 Bologna, Italy.. katia.scotlandi@ior.it) . European journal of cancer (Oxford, England : 1990), (2005 Jun) 41 (9) 1349-61. Journal code: 9005373. ISSN: 0959-8049. Pub. country: England: United Kingdom. Language: English.
AB Expression of HER2 was evaluated by immunohistochemical techniques in 84

osteosarcoma (OS) and 113 Ewing's sarcoma (ES) paraffin-embedded tumour biopsies. HER2 gene status was also assessed in a panel of cell lines as well as in vitro efficacy of trastuzumab (a humanised antibody directed against HER2) as single agent or in combination with the insulin-like growth factor I receptor (IGF-IR) IR3 antibody. Overexpression of HER2 was present in 32% of OS and 16% of ES and was significantly associated with the increased expression of P-glycoprotein, a surface molecule responsible for multidrug resistance. Event-free survival analyses revealed a prognostic value for HER2 and/or P-glycoprotein expression in OS, but not in ES. However, despite its prognostic relevance, no therapeutic effectiveness was observed pre-clinically for trastuzumab-driven therapy, in both OS or ES cell lines, unless the antibody was associated with **anti-IGF-IR** targeting strategies. Therefore, the therapeutic potential of trastuzumab in these neoplasms may be better exploited in combined treatments with **anti-IGF-IR** approaches.

L11 ANSWER 9 OF 43 MEDLINE on STN DUPLICATE 4

2005428011. PubMed ID: 16093437. Inhibition of insulin-like growth factor-I receptor (IGF-IR) signaling and tumor cell growth by a fully human neutralizing **anti-IGF-IR** antibody.

Wang Yan; Hailey Judith; Williams Denise; Wang Yaolin; Lipari Philip; Malkowski Michael; Wang Xiaoying; Xie Lei; Li Guanghua; Saha Deba; Ling Wai Lam W; Cannon-Carlson Susan; Greenberg Robert; Ramos Robert A; Shields Robert; Presta Leonard; Brams Peter; Bishop W Robert; Pachter Jonathan A. (Department of Oncology, Schering-Plough Research Institute, 2015 Galloping Hill Road, K15-4600, Kenilworth, NJ 07033, USA.. yan.wang@spcorp.com) . Molecular cancer therapeutics, (2005 Aug) 4 (8) 1214-21. Journal code: 101132535. ISSN: 1535-7163. Pub. country: United States. Language: English.

AB Insulin-like growth factor-I receptor (IGF-IR) plays an important role in tumor cell growth and survival. On ligand stimulation, IGF-IR, a receptor tyrosine kinase, phosphorylates tyrosine residues on two major substrates, IRS-1 and Shc, which subsequently signal through the Ras/mitogen-activated protein kinase and phosphatidylinositol 3-kinase/AKT pathways. Here, we describe the characterization of a fully human **anti-IGF-IR** monoclonal antibody 19D12 that inhibits IGF binding and autophosphorylation of both IGF-IR/IGF-IR homodimers and IGF-IR/insulin receptor heterodimers. 19D12 does not recognize insulin receptor homodimers. In addition to inhibiting IGF-IR autophosphorylation, 19D12 also inhibits IRS-1 phosphorylation and activation of the major downstream signaling molecules AKT and extracellular signal-regulated kinase 1/2. Furthermore, the antibody down-regulates the total IGF-IR protein level and can exhibit antibody-dependent cellular cytotoxicity activity against a non-small cell adenocarcinoma cell line in vitro in the presence of isolated human natural killer cells. 19D12 binds tightly to the receptor, with an affinity of 3.8 pmol/L as measured by KinExA. In cell culture, 19D12 inhibits proliferation and soft agar growth of various tumor cell lines. In vivo, 19D12 inhibits the tumor growth of a very aggressive human ovarian tumor xenograft model A2780. These data support the development of this **anti-IGF-IR** monoclonal antibody as a promising anticancer agent.

L11 ANSWER 10 OF 43 MEDLINE on STN

2005323941. PubMed ID: 15972147. Expression of insulin-like growth factor receptor type I in marrow nucleated cells from hematologic malignancies and its anti-apoptotic effect. He Qi; Li Xiao; Tao Ying; Liu Yi-Zhi; Yang Lian-Ping; Ying Shao-Xu. (Department of Hematology, The Sixth Hospital, Shanghai 200233, China.) Zhongguo shi yan xue ye xue za zhi / Zhongguo bing li sheng li xue hui = Journal of experimental hematology / Chinese Association of Pathophysiology, (2005 Jun) 13 (3) 483-7. Journal code: 101084424. ISSN: 1009-2137. Pub. country: China. Language: Chinese.

AB To explore the expression of insulin-like growth factor receptor type I (IGF-IR) and its relationship to apoptosis in hematopoietic cells of MDS and AML marrow, bone marrow nucleated cells from 16 patients with

myelodysplastic syndrome (MDS) and 16 patients with acute myeloid leukemia (AML) were collected for analysis, respectively. Another 16 normal donors' marrow samples were taken as controls. Immunocytochemical method (APAAP) and TdT-mediated dUTP nick end labeling (TUNEL) fluorescence were used simultaneously on cytospins of nucleated cells from these patients. Then, the ratios of IGF-IR positive cells and apoptosis cells in all nucleated cells were counted separately. The results showed that (1) there was a higher IGF-IR expression rate (56.8 +/- 14.3)% in nucleated cells of MDS marrow than that in normal marrow (40.4 +/- 9.6)% ($P < 0.01$). Also IGF-IR positive rate in AML marrow (86.8 +/- 13.8)% was significantly higher than that in normal marrow ($P < 0.01$). Furthermore, IGF-IR had higher expression in AML marrow when compared to MDS marrow ($P < 0.01$); (2) apoptosis in nucleated cells of MDS marrow (5.4 +/- 3.0)% was significantly higher than that in normal marrow (1.2 +/- 0.9)% ($P < 0.01$) and AML marrow (0.3 +/- 0.4)% ($P < 0.01$), while there was less apoptosis in AML marrow than that in normal marrow ($P < 0.01$); (3) apoptosis occurred mainly in IGF-IR negative cells (9.0 +/- 4.8)% and less in IGF-IR positive cells (1.4 +/- 2.4)% ($P < 0.01$). IGF-IR expression showed negative correlation with apoptosis ($r = -0.852$, $P < 0.01$); (4) IGF-IR of MDS nucleated cells in RAEB/RAEB-t/CMML expressed higher than that in RA/RAS (64.1 +/- 3.2% vs 53.5 +/- 16.2%) subgroup, although no significant difference was found ($P > 0.05$); and apoptosis in RAEB/RAEB-t/CMML subgroup was lower than that in RA/RAS cases (3.1 +/- 2.1% vs 6.4 +/- 2.8%) ($P < 0.05$); (5) IGF-IR positive rate in nucleated cells of MDS and AML marrow showed positive correlation with blast rate ($r = 0.677$; $P < 0.01$). It is concluded that there is overexpression of IGF-IR in marrow nucleated cells in MDS and AML cases. And it seems that the overexpression of IGF-IR may suggest some malignant proliferation tendency and suppress cell apoptosis through some mechanism in these malignant hematologic ailments. So, **anti-IGF-IR** will become a new approach for therapy of MDS and AML.

L11 ANSWER 11 OF 43 MEDLINE on STN DUPLICATE 5

2004574411. PubMed ID: 15386423. A recombinant humanized anti-insulin-like growth factor receptor type I antibody (h7C10) enhances the antitumor activity of vinorelbine and anti-epidermal growth factor receptor therapy against human cancer xenografts. Goetsch Liliane; Gonzalez Alexandra; Leger Olivier; Beck Alain; Pauwels Petrus J; Haeuw Jean Francois; Corvaia Nathalie. (Centre d'Immunologie Pierre Fabre, 5 Avenue Napoleon III, 74160, St. Julien en Genevois, France.. Liliane.Goetsch@pierre-fabre.com) . International journal of cancer. Journal international du cancer, (2005 Jan 10) 113 (2) 316-28. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB Interaction of insulin-like growth factor receptor I (IGF-IR) with its ligands has been reported to induce cell proliferation, transformation and blockade of cell apoptotic functions. IGF-IR is overexpressed on numerous tumor cell types and its blockade could be of importance for anti-cancer therapy. We have generated a humanized **anti-IGF-IR** antibody h7C10 that blocks in vitro IGF-I and IGF-II-induced cell proliferation of MCF-7 breast cancer cells. Analysis of the IGF-I transduction cascade demonstrated that the humanized **anti-IGF-IR** antibody and its murine parental form block IGF-I-induced tyrosine phosphorylation, both its beta-chain and IRS-1 tyrosine phosphorylation. This presumably leads to cell cycle arrest and, consequently, growth inhibition. Treatment of nude mice bearing either human breast cancer cells (MCF-7) or non small lung cancer cells (A549) with h7C10, or its murine parental form 7C10, inhibited significantly tumor growth. An almost complete inhibition of A549 tumor growth was observed when mice were treated with the **anti-IGF-IR** antibody combined with either a chemotherapeutic agent, Vinorelbine or an anti-epidermal growth factor receptor (EGFR) antibody, 225. Combined therapy prolonged significantly the life span of mice in an orthotopic in vivo model of A549; the combination of the **anti-IGF-IR** antibody with an anti-EGFR antibody was superior to the Vinorelbine combination. The present results indicate that the

humanized **anti-IGF-IR** antibody h7C10 has a great potential for cancer therapy when combined with either a chemotherapeutic agent or an antibody that targets other growth factor receptors, such as the epidermal growth factor receptor.

L11 ANSWER 12 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN
2004:799597 Document No. 141:312944 Phagemid library-derived human **anti-IGF-IR** scFv antibodies for diagnosis and treatment of cancers. Morton, Philip A.; Arbuckle, J. Alan; Bailey, Karen J.; Nicastro, Peter J.; Runnels, Herbert A. (Pharmacia Corporation, USA). PCT Int. Appl. WO 2004083248 A1 20040930, 259 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-IB646 20040304. PRIORITY: US 2003-2003/PV455094 20030314.
AB Human, chimeric, humanized, bispecific antibodies and fragments specific for insulin-like growth factor I receptor (IGF-IR) are provided. The antibodies and fragments thereof may block binding of IGF-I or IGF-II to IGF-IR. Antagonist antibodies can be employed to block binding of IGF-I to IGF-IR or substantially inhibit IGF-IR activation. The IGF-IR antibodies may be included in pharmaceutical compns., articles of manufacture, or kits. Methods of treating cancer, inflammation, and pathol. liver conditions, using the IGF-IR antibodies are also provided.

L11 ANSWER 13 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN
2004:696273 Document No. 141:205683 Therapeutic uses of human anti-human insulin-like growth factor I receptor antibodies. Cohen, Bruce David; Bedian, Vahe; Wang, Huifen Faye; Obrocea, Mihail; Gomez-Navarro, Jesus; Cusmano, John Daniel; Guyot, Deborah Jean; Page, Kelly Lynn (Pfizer Products Inc., USA). PCT Int. Appl. WO 2004071529 A2 20040826, 105 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-IB366 20040203. PRIORITY: US 2003-2003/PV447353 20030213.
AB The present invention relates to a therapeutic method comprising administering anti-human insulin-like growth factor I receptor (IGF-IR) antibodies, particularly fully human **anti-IGF-IR** antibodies to a subject for the treatment of certain disorders, such as cancer, preferably in conjunction with administration of another therapeutic agent. In preferred embodiment **anti-IGF-IR** antibodies comprise heavy chain from the human VH DP-35, VIV-4/4.35, VH DP-47, or VH DP-71 gene, and light chain from the A27, A30, or 012 gene. The invention further relates to pharmaceutical compns. comprising these antibodies and methods of using the antibodies and compns. thereof for treatment. Demonstrated that the antibodies of the invention are able to target the IGF-IR in vivo and in vitro. Also demonstrated that a single treatment with antiboy 2.13.2 alone inhibited the growth of IGF-IR transfected NIH-3T3 cell-induced tumors.

L11 ANSWER 14 OF 43 MEDLINE on STN DUPLICATE 6
2004381305. PubMed ID: 15208677. Overexpression of CEACAM6 promotes insulin-like growth factor I-induced pancreatic adenocarcinoma cellular invasiveness. Duxbury Mark S; Ito Hiromichi; Benoit Eric; Zinner Michael J; Ashley Stanley W; Whang Edward E. (Department of Surgery, Brigham and

Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA.) Oncogene, (2004 Jul 29) 23 (34) 5834-42. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB Carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) is a glycosylphosphatidylinositol-linked immunoglobulin superfamily member that is overexpressed in a variety of human cancers. We have recently reported that suppression of CEACAM6 expression impairs pancreatic adenocarcinoma progression in vivo. In order to characterize the mechanisms through which CEACAM6 influences the malignant phenotype, CEACAM6-overexpressing Capan2 pancreatic adenocarcinoma cells were established by stable transfection. We determined the effect of CEACAM6 overexpression on cellular invasiveness towards insulin-like growth factor I (IGF-I), a peptide of critical importance in pancreatic cancer malignant cellular behavior and tumor progression. IGF-I-induced cellular invasiveness and IGF-IR expression were significantly increased in clones overexpressing CEACAM6. Using inhibitory **anti-IGF-IR** antibody, a requirement for IGF-IR signaling in the enhanced invasiveness towards IGF-I induced by CEACAM6 overexpression was confirmed. CEACAM6-overexpressing clones exhibited increased Akt and c-Src kinase activities, as well as higher levels of matrix metalloproteinase-2 (MMP-2) expression and activity in the presence of IGF-I. While Akt kinase is both necessary and sufficient to induce IGF-IR upregulation, c-Src kinase activity is necessary, but alone is insufficient to upregulate IGF-IR expression. CEACAM6 is an important determinant of pancreatic adenocarcinoma malignant cellular behavior and, together with its downstream targets, warrants further investigation as a therapeutic target in this disease.

L11 ANSWER 15 OF 43 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2005:91026 Document No.: PREV200500090886. Expression of insulin-like growth factor 1 receptor in primary breast cancer: Immunohistochemical analysis. Shimizu, Chikako [Reprint Author]; Hasegawa, Tadashi; Tani, Yoichi; Takahashi, Fumiaki; Takeuchi, Masahiro; Watanabe, Toru; Ando, Masashi; Katsumata, Noriyuki; Fujiwara, Yasuhiro. Natl Canc Ctr Hosp, 5-1-1 Tsukiji, Tokyo, 1040045, Japan. Human Pathology, (December 2004) Vol. 35, No. 12, pp. 1537-1542. print.
ISSN: 0046-8177 (ISSN print). Language: English.

AB Insulin-like growth factor-1 receptor (IGF-1R) has been implicated in regulation in tumor growth. The results of previous studies performed by radioimmunoassay are conflicting, and the prognostic significance of IGF-1R expression in primary breast cancer is still controversial. IGF-1R expression was evaluated in formalin-fixed, paraffin-embedded tissue of 210 primary breast cancer patients by using anti-IGF-1R antibody. The clinicopathologic variables and 5-year disease-free survival were studied, and their correlations between IGF-1R expressions were investigated. IGF-1R overexpression was observed in 43.8% of tumors. IGF-1R overexpression had no correlation with prognosis or with other clinicopathologic parameters, such as age, tumor size, nodal status, histologic grade, hormone receptor status, and human epidermal growth factor 2 status. Though its prognostic value in breast cancer is limited, immunohistochemical evaluation of IGF-1R by using this monoclonal antibody may be useful in translational research using archived material.

L11 ANSWER 16 OF 43 MEDLINE on STN DUPLICATE 7

2004620558. PubMed ID: 15595626. Role of estrogen receptor alpha in modulating IGF-I receptor signaling and function in breast cancer. Surmacz E; Bartucci M. (Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA 19107, USA.. eva.surmacz@jefferson.edu) . Journal of experimental & clinical cancer research : CR, (2004 Sep) 23 (3) 385-94. Ref: 103. Journal code: 8308647. ISSN: 0392-9078. Pub. country: Italy. Language: English.

AB The insulin-like growth factor I (IGF-I) receptor (IGF-IR) is a

multifunctional transmembrane tyrosine kinase that has been implicated in neoplastic transformation. The tumorigenic potential of IGF-IR relies on its strong anti-apoptotic and mitogenic activity. The growth and survival signals of IGF-IR are mediated through multiple intracellular pathways, many of which emanate from insulin receptor substrate 1 (IRS-1). In hormone-dependent breast cancer cells, IGF-IR and IRS-1 are often co-expressed with the estrogen receptor alpha (ERalpha), and IGF-I and ER systems are engaged in a powerful functional cross-talk. Most notably, activation of ERalpha upregulates the expression of IRS-1, IGF-IR, and IGF-1, which results in amplification of IGF-I responses. Reciprocally, stimulation of IGF-IR increases the phosphorylation and activity of ERalpha. In contrast, in ERalpha-negative breast cancer cells and tumors, the levels of IGF-IR and IRS-1 are often decreased and IGF-I is non-mitogenic. Our data suggest that defective IGF-IR signaling in ERalpha-negative cells is related, at least in part, to improper activation of the IRS-1/PI-3K/Akt/GSK-3 pathway and lack of Rb1 phosphorylation. These defects are partially reversed by re-expression of ERalpha. Interestingly, some non-mitogenic IGF-I responses, such as migration and invasion are retained in the absence of ERalpha, suggesting that IGF-IR function in breast cancer cells might depend on the ERalpha status. The understanding of how ERalpha may dictate IGF-I responses will help in devising rational **anti-IGF-IR** strategies for breast cancer treatment.

L11 ANSWER 17 OF 43 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

2004:53866 The Genuine Article (R) Number: 759XE. EphA3 is induced by CD28 and 1GF-1 and regulates cell adhesion. Smith L M; Walsh P T; Rudiger T; Cotter T G; Mc Carthy T V; Marx A; O'Connor R (Reprint). Natl Univ Ireland, Biosci Inst, Dept Biochem, Cork, Ireland (Reprint); Univ Wurzburg, Dept Pathol, D-8700 Wurzburg, Germany. EXPERIMENTAL CELL RESEARCH (15 JAN 2004) Vol. 292, No. 2, pp. 295-303. ISSN: 0014-4827. Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Stimulation of CD28 alone has been shown to regulate cytokine gene transcription and expression of the type I insulin-like growth factor receptor (IGF-1R) in lymphocytes. In this study, the ephrin receptor tyrosine kinase ephA3, was identified as a new CD28-responsive gene in Jurkat cells by using a human cytokine/receptor array. EphA3 was not detected in normal peripheral T cells, in any subset of thymus-derived developing T cells, or in Hodgkin's lymphoma. However, contrary to previous findings, EphA3 was detected in a panel of T-cell lymphomas. Stimulation of Jurkat cells with ephrin-A5 resulted in loss of cell adhesion to fibronectin and recruitment of the adapter protein CrkII to EphA3. Interestingly, EphA3 expression in CD28-stimulated Jurkat cells was enhanced by IGF-1 or by overexpression of the IGF-IR, and was suppressed by **anti-IGF-IR** blocking antibodies. The data suggest that CD28- and IGF-1-regulated expression of EphA3 is associated with adherence and that it may be involved in the motility of malignant T cells. (C) 2003 Elsevier Inc. All rights reserved.

L11 ANSWER 18 OF 43 MEDLINE on STN DUPLICATE 8

2003466597. PubMed ID: 14528284. Growth factor receptors as therapeutic targets: strategies to inhibit the insulin-like growth factor I receptor. Surmacz Eva. (Kimmel Cancer Center, Thomas Jefferson University, 233 S 10th St., BLSB 631, Philadelphia, PA 19107, USA.. eva.surmacz@mail.tju.edu) . Oncogene, (2003 Sep 29) 22 (42) 6589-97. Ref: 110. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB Neoplastic transformation is often related to abnormal activation of growth factor receptors and their signaling pathways. The concept of targeting specific tumorigenic receptors and/or signaling molecules has been validated by the development and successful clinical application of

drugs acting against the epidermal growth factor receptor 2 (HER2/neu, Erb2), the epidermal growth factor receptor 1 (EGFR, HER1), the Brc-Abl kinase, the platelet-derived growth factor receptor, and c-kit. This review will focus on the next promising therapeutic target, the insulin-like growth factor I receptor (IGF-IR). IGF-IR has been implicated in a number of neoplastic diseases, including several common carcinomas. From a pharmaceutical standpoint, of particular importance is that IGF-IR appears to be required for many transforming agents (genetic, viral, chemical) to act, but is not obligatory for the function of normal adult cells. The tumorigenic potential of IGF-IR is mediated through its antiapoptotic and transforming signaling, and in some cases through induction of prometastatic pathways. Preclinical studies demonstrated that downregulation of IGF-IR reversed the neoplastic phenotype and sensitized cells to antitumor treatments. The strategies to block IGF-IR function employed **anti-IGF-IR** antibodies, small-molecule inhibitors of the IGF-IR tyrosine kinase, antisense oligodeoxynucleotides and antisense RNA, small inhibitory RNA, triple helix, dominant-negative mutants, and various compounds reducing ligand availability. The experience with these strategies combined with the knowledge gained with current anti-growth factor receptor drugs should streamline the development of **anti-IGF-IR** therapeutics.

L11 ANSWER 19 OF 43 EMBASE

2003453015 EMBASE Growth factor receptors as therapeutic targets: Strategies to inhibit the insulin-like growth factor I receptor. Surmacz E.. E. Surmacz, Kimmel Cancer Center, Thomas Jefferson University, BLSB 631, 233 S 10th St., Philadelphia, PA 19107, United States. eva.surmacz@mail.tju.edu. Oncogene Vol. 22, No. 43, pp. 6589-6597 2 Oct 2003.

Refs: 110.

ISSN: 0950-9232. CODEN: ONCNES

Pub. Country: United Kingdom. Language: English. Summary Language: English.

ED Entered STN: 20031204

AB Neoplastic transformation is often related to abnormal activation of growth factor receptors and their signaling pathways. The concept of targeting specific tumorigenic receptors and/or signaling molecules has been validated by the development and successful clinical application of drugs acting against the epidermal growth factor receptor 2 (HER2/neu, Erb2), the epidermal growth factor receptor 1 (EGFR, HER1), the Brc-Abl kinase, the platelet-derived growth factor receptor, and c-kit. This review will focus on the next promising therapeutic target, the insulin-like growth factor I receptor (IGF-IR). IGF-IR has been implicated in a number of neoplastic diseases, including several common carcinomas. From a pharmaceutical standpoint, of particular importance is that IGF-IR appears to be required for many transforming agents (genetic, viral, chemical) to act, but is not obligatory for the function of normal adult cells. The tumorigenic potential of IGF-IR is mediated through its antiapoptotic and transforming signaling, and in some cases through induction of prometastatic pathways. Preclinical studies demonstrated that downregulation of IGF-IR reversed the neoplastic phenotype and sensitized cells to antitumor treatments. The strategies to block IGF-IR function employed **anti-IGF-IR** antibodies, small-molecule inhibitors of the IGF-IR tyrosine kinase, antisense oligodeoxynucleotides and antisense RNA, small inhibitory RNA, triple helix, dominant-negative mutants, and various compounds reducing ligand availability. The experience with these strategies combined with the knowledge gained with current anti-growth factor receptor drugs should streamline the development of **anti-IGF-IR** therapeutics.

L11 ANSWER 20 OF 43 MEDLINE on STN DUPLICATE 9

2003402761. PubMed ID: 12941837. An anti-insulin-like growth factor I

receptor antibody that is a potent inhibitor of cancer cell proliferation. Maloney Erin K; McLaughlin Jennifer L; Dagdigian Nancy E; Garrett Lisa M; Connors Katherine M; Zhou Xiao-Mai; Blattler Walter A; Chittenden Thomas; Singh Rajeeva. (ImmunoGen, Inc., 128 Sidney Street, Cambridge, Massachusetts 02139, USA.) Cancer research, (2003 Aug 15) 63 (16) 5073-83. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB An antagonistic monoclonal antibody, designated EM164, has been developed which binds specifically to the human insulin-like growth factor I receptor (IGF-IR) and inhibits the proliferation and survival functions of the receptor in cancer cells. EM164 was initially selected by a rapid cell-based screen of hybridoma supernatants to identify antibodies that bind to IGF-IR but not to the homologous insulin receptor and that show maximal inhibition of IGF-I-stimulated autophosphorylation of IGF-IR. EM164 binds tightly to IGF-IR with a dissociation constant K(d) of 0.1 nM, inhibits binding of IGF-I and antagonizes its effects on cells completely, and has no agonistic activity on its own. EM164 inhibits IGF-I-, IGF-II-, and serum-stimulated proliferation and survival of diverse human cancer cell lines in vitro, including breast, lung, colon, cervical, ovarian, pancreatic, melanoma, prostate, neuroblastoma, rhabdomyosarcoma, and osteosarcoma cancer lines. It also suppresses the autocrine or paracrine proliferation of several cancer cell lines. EM164 was the most potent antagonistic **anti-IGF-IR** antibody tested when compared with several commercially available antibodies. The in vitro inhibitory effect could be extended to in vivo tumor models, where EM164 caused regression of established BxPC-3 human pancreatic tumor xenografts in SCID mice. The antitumor effect of treatment with EM164 could be enhanced by combining it with the cytotoxic agent gemcitabine. These data support the development of EM164 as a candidate therapeutic agent that targets IGF-IR function in cancer cells.

L11 ANSWER 21 OF 43 MEDLINE on STN DUPLICATE 10

2003098500. PubMed ID: 12578538. Steroidogenic responses of pig corpora lutea to insulin-like growth factor I (IGF-I) throughout the oestrous cycle. Miller E A; Ge Z; Hedgpeth V; Gadsby J E. (Department of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606, USA.) Reproduction (Cambridge, England), (2003 Feb) 125 (2) 241-9. Journal code: 100966036. ISSN: 1470-1626. Pub. country: England: United Kingdom. Language: English.

AB This study was designed to investigate the roles of insulin-like growth factor I (IGF-I), IGF-type I receptor (IGF-IR) and IGF-binding proteins (IGFBPs) in regulating progesterone secretion by pig corpora lutea during the oestrous cycle, and the signal transduction pathways involved in mediating the steroidogenic actions of IGF-I. Corpora lutea were collected on days 4, 7, 10, 13 and 15 or 16 of the oestrous cycle, enzyme dissociated and the luteal cells were cultured for 24 h in Medium 199 with IGF-I (0-100 ng ml(-1)), long R(3)-IGF-I (0-100 ng ml(-1)), anti-IGF-I (Sm 1.2B; 0-10 microg ml(-1)), **anti-IGF-IR** (alphaIR3; 0-2 microg ml(-1)), or IGF-I signal transduction pathway inhibitors (phosphatidylinositol (PI)-3-kinase: 100 nmol Wortmannin l(-1) and 10 micromol LY 294002 l(-1); MAP kinase: 50 micromol PD 98059 l(-1)) to investigate their effects on IGF-I (100 ng ml(-1)) stimulated progesterone secretion. Pig luteal cells displayed dose-dependent responses to IGF-I and long R(3)-IGF-I on days 4 and 7 of the oestrous cycle, but not on days 10-16. There was no difference in the ED(50) or V(max) (maximal response) values between IGF-I and long R(3)-IGF-I. Neither anti-IGF-I nor **anti-IGF-IR** had significant effects on progesterone secretion, at any dose or day. Wortmannin and LY 294002 blocked IGF-I stimulated progesterone secretion, but PD 98059 was without effect. Finally, IGF-I (6 microg) infused into the ovary on day 7 in vivo significantly increased progesterone secretion within 45 min of infusion. The conclusions of this study are: (1) IGF-I has steroidogenic actions only on 'young' (days 4-7) pig corpora lutea; (2) endogenous IGF-I and IGFBP are insufficient to modulate progesterone secretion in vitro; and (3) the steroidogenic actions of IGF-I are

mediated via PI-3-kinase.

L11 ANSWER 22 OF 43 MEDLINE on STN DUPLICATE 11
2003033463. PubMed ID: 12540483. Insulin-like growth factor-I receptor-mediated vasculogenesis/angiogenesis in human lung development. Han Robin N N; Post Martin; Tanswell A Keith; Lye Stephen J. (CIHR Group in Development and Fetal Health, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Canada, M5G 1X5.. hanrobin@aol.com) . American journal of respiratory cell and molecular biology, (2003 Feb) 28 (2) 159-69. Journal code: 8917225. ISSN: 1044-1549. Pub. country: United States. Language: English.
AB The structural and functional development of the pulmonary system is dependent upon appropriate early vascularization of the embryonic lung. Our previous in vitro studies in a rat model indicated that insulin-like growth factor-I (IGF-I) is a potent angiogenic agent for fetal lung endothelial cells. To assess its role on human vascular lung development, we first examined the expression of IGF-I/II and IGF receptor type I (IGF-IR) in human embryonic and fetal lung tissues at 4-12 wk of gestation. Immunohistochemical and in situ hybridization studies revealed the presence of IGF-I/II-IGF-IR ligands and mRNA transcripts in embryonic lungs as early as 4 wk gestation. Immunotargeting using an **anti -IGF-IR** neutralizing antibody on human fetal lung explants demonstrated a significant blockade of IGF-IR signaling. Inactivation of IGF-IR resulted in a loss of endothelial cells, accompanied by dramatic changes in fetal lung explant morphology. Terminal transferase dUTP end-labeling assay and TEM studies of **anti-IGF-IR**-treated lungs demonstrated numerous apoptotic mesenchymal cells. Rat embryonic lung explant studies further validated the importance of the IGF-IGF-IR system for lung vascular development. These data provide the first demonstration of IGF-I/II expression in the human lung in early gestation and indicate that the IGF family of growth factors, acting through the IGF-IR, is required as a survival factor during normal human lung vascularization.

L11 ANSWER 23 OF 43 CAPLUS COPYRIGHT 2006 ACS on STN
2002:293968 Document No. 136:291347 Immunochemical method for diagnosing and classifying carcinomas, based on the detection of IGF-IRβ and IRS-1. Schnarr, Bernd; Mayer, Doris (Deutsches Krebsforschungszentrum, Germany). PCT Int. Appl. WO 2002031500 A2 20020418, 27 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2001-DE3988 20011010. PRIORITY: DE 2000-10050338 20001011.
AB The invention relates to an immunochem. method for diagnosing and/or classifying carcinomas, preferably mammary carcinomas. The detection process is carried out by using an **anti-IGF-IR** β and/or anti-IRS-1 antibody. A reduced IRS-1 and/or IGF-IRβ expression is a diagnostic indication of a slightly differentiated carcinoma (stage 3), while a high IRS-1 and/or IGF-IRβ expression is a diagnostic indication of a well or moderately differentiated carcinoma (stages 1 and 2).

L11 ANSWER 24 OF 43 MEDLINE on STN DUPLICATE 12
2002382601. PubMed ID: 12127559. Expression of insulin-like growth factors IGF-I and IGF-II, and their receptors during the growth and megakaryocytic differentiation of K562 cells. Aro Aapo L A; Savikko Johanna; Pulkkinen Ville; von Willebrand Eva. (Transplantation Laboratory, Haartman Institute, Helsinki University Central Hospital, University of Helsinki, P.O. Box 21, Haartmaninkatu 3, Helsinki, Finland.. aapo.aro@helsinki.fi) . Leukemia research, (2002 Sep) 26 (9) 831-7. Journal code: 7706787. ISSN: 0145-2126. Pub. country: England: United Kingdom. Language: English.
AB Insulin-like growth factors (IGFs) I and II are critical regulators of cell proliferation and differentiation and most of the growth promoting properties of both ligands are mediated by IGF-I receptor (IGF-IR). In the present study we have investigated the role of IGFs in K562 cell line during normal growth and 12-O-tetradecanoyl-phorbol-13-acetate

(TPA)-induced megakaryocytic differentiation. Abundant expression of IGF-I, IGF-II and IGF-IR was demonstrated in resting cells and exogenous IGF-I and IGF-II increased 3H-thymidine incorporation in a dose dependent manner. In contrast, we found that basal growth of the cells was inhibited by using **anti-IGF-IR** mAb.
Furthermore, also IGF-I and IGF-II induced DNA synthesis was significantly suppressed by **anti-IGF-IR** mAb. During
megakaryocytic differentiation, expression of IGF-IR increased during first 12h, but after that the expression started to decrease together with IGF-I. Taken together, our data suggest that autocrine production of IGF-I and IGF-II may via IGF-IR play a significant role in the growth and megakaryocytic differentiation of K562 cells.

L11 ANSWER 25 OF 43 MEDLINE on STN DUPLICATE 13
2002124743. PubMed ID: 11839539. Insulin-like growth factor I receptor is downregulated after alveolarization in an apoptotic fibroblast subset. Srinivasan Suseela; Strange Jennifer; Awonusonu Feyisola; Bruce Margaret C. (Department of Pediatrics, University of Kentucky Medical School, Lexington, Kentucky 40536, USA.) American journal of physiology. Lung cellular and molecular physiology, (2002 Mar) 282 (3) L457-67. Journal code: 100901229. ISSN: 1040-0605. Pub. country: United States. Language: English.

AB After alveolar formation, >20% of interstitial lung fibroblasts undergo apoptosis, a process that is of critical importance for normal lung maturation. The immature lung contains two morphologically distinct fibroblast populations, lipid-filled interstitial fibroblasts (LIF) and non-LIF (NLIF), which differ with respect to contractile protein content, proliferative capacity, and expression of mRNAs for fibronectin and types I and III collagen, but not tropoelastin. After alveolarization, apoptosis occurs in only one fibroblast population, the LIF. Using flow cytometry to analyze fibroblasts stained with a lipophilic, fluorescent dye, we identified a subset, designated LIF(-), that contained fewer lipid droplets. Unlike LIF that retain lipid, LIF(+), the LIF(-) do not undergo apoptosis after alveolarization. In LIF(+), apoptosis was correlated with downregulation of insulin-like growth factor I receptor (IGF-IR) mRNA and cell surface protein expression. Treatment with **anti-IGF-IR** decreased total lung fibroblast survival ($P = 0.05$) as did treatment with the phosphatidylinositol 3-kinase inhibitor LY-294002 and the ras-raf-mitogen-activated protein kinase inhibitor PD-98059 ($P < 0.002$), which block IGF-I/insulin receptor survival pathways. These observations implicate downregulation of IGF-IR expression in fibroblast apoptosis after alveolar formation.

L11 ANSWER 26 OF 43 MEDLINE on STN DUPLICATE 14
2003057498. PubMed ID: 12568311. Sequence dependence of C5-propynyl-dU,dC-phosphorothioate oligonucleotide inhibition of the human IGF-I receptor: mRNA, protein, and cell growth. Fogarty Rhys D; McKean Sandra C; White Paul J; Atley Lynne M; Werther George A; Wraight Christopher J. (Centre for Hormone Research, Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, Victoria 3052, Australia.) Antisense & nucleic acid drug development, (2002 Dec) 12 (6) 369-77. Journal code: 9606142. ISSN: 1087-2906. Pub. country: United States. Language: English.

AB Human keratinocytes are highly responsive to mitogenic and antiapoptotic signaling by the insulin-like growth factor-I receptor (IGF-IR). IGF-IR hyperstimulation is a feature of hyperplastic skin conditions, making the IGF-IR an appealing target for antisense therapeutic intervention. In this study, we used a C5-propynyl-dU,dC-phosphorothioate oligo-2'-deoxyribonucleotide antisense 15-mer to the human IGF-IR mRNA, along with liposome transfection, to inhibit IGF-IR activity in a human keratinocyte cell line and demonstrated potent inhibition of cell growth despite the presence of serum. To investigate the sequence specificity of these effects and to establish the concentration range over which a purely antisense effect could be demonstrated, we introduced 1, 2, 4, 8, and 15 base mismatches into the oligonucleotide and analyzed changes in

inhibitory efficacy. In the 10-30 nM concentration range, the introduction of 1 and 2 mismatches into the middle of the 15-mer only modestly affected inhibitory efficacy, whereas >4 mismatches profoundly reduced mRNA, protein, and growth-inhibitory effects. From these results, we conclude that (1) sequence-specific antisense inhibition of IGF-IR activity in keratinocytes is achievable, (2) potent **anti-IGF-IR** antisense inhibition can be achieved in vitro at concentrations as low as 10 nM, and (3) a sequence-dependent mechanism is likely to underpin the observed in vivo therapeutic effects (Wraight et al. Nat. Biotechnol. 2000;18:521) of these antisense oligonucleotides (AS-ODN) in cutaneous hyperplastic disorders, such as psoriasis.

L11 ANSWER 27 OF 43 MEDLINE on STN DUPLICATE 15

2002341319. PubMed ID: 12083381. Hypertrophy of cultured adult rat ventricular cardiomyocytes induced by antibodies against the insulin-like growth factor (IGF)-I or the IGF-I receptor is IGF-II-dependent. Huang Chih-Yang; Hao Ling-Yang; Buetow Dennis E. (Department of Molecular and Integrative Physiology, University of Illinois, Urbana 61801, USA.) Molecular and cellular biochemistry, (2002 Apr) 233 (1-2) 65-72. Journal code: 0364456. ISSN: 0300-8177. Pub. country: Netherlands. Language: English.

AB Antibodies against the insulin-like growth factor-I (IGF-I) or the IGF-I receptor (IGF-IR) directly initiate a rapid (within 6 h) hypertrophy of isolated adult rat ventricular cardiomyocytes cultured in the absence of serum. Further, cardiomyocytes treated with either of these agonistic antibodies upregulate the expression of their genes for insulin-like growth factor-II (IGF-II) and the IGF-II receptor (IGF-IIR). Genistein, an inhibitor of the tyrosine kinase IGF-IR, also induces the cardiomyocytes to hypertrophy. Anti-IGF-II antibody inhibits the cardiomyocyte hypertrophy induced by anti-IGF-I and **anti-IGF-IR** antibodies or by genistein. Results are consistent with a model in which local production of IGF-II is upregulated when the IGF-IR signaling pathway is blocked and in which an IGF-II-mediated pathway, likely involving the IGF-IIR, then stimulates hypertrophy of the cardiomyocytes.

L11 ANSWER 28 OF 43 EMBASE

2002218553 EMBASE Insulin-like growth factor I receptor is downregulated after alveolarization in an apoptotic fibroblast subset. Srinivasan S.; Strange J.; Awonusonu F.; Bruce M.C.. M.C. Bruce, Dept. of Pediatrics, Div. of Neonatology, Univ. of Kentucky Medical School, Lexington, KY 40536, United States. mbruce@uky.edu. American Journal of Physiology - Lung Cellular and Molecular Physiology Vol. 282, No. 3 26-3, pp. L457-L467 2002.
Refs: 30.
ISSN: 1040-0605. CODEN: APLPE7
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20020708

AB After alveolar formation, >20% of interstitial lung fibroblasts undergo apoptosis, a process that is of critical importance for normal lung maturation. The immature lung contains two morphologically distinct fibroblast populations, lipid-filled interstitial fibroblasts (LIF) and non-LIF (NLIF), which differ with respect to contractile protein content, proliferative capacity, and expression of mRNAs for fibronectin and types I and III collagen, but not tropoelastin. After alveolarization, apoptosis occurs in only one fibroblast population, the LIF. Using flow cytometry to analyze fibroblasts stained with a lipophilic, fluorescent dye, we identified a subset, designated LIF(-), that contained fewer lipid droplets. Unlike LIF that retain lipid, LIF(+), the LIF(-) do not undergo apoptosis after alveolarization. In LIF(+), apoptosis was correlated with downregulation of insulin-like growth factor I receptor (IGF-IR) mRNA and cell surface protein expression. Treatment with **anti-IGF-IR** decreased total lung fibroblast survival (P = 0.05) as did treatment with the phosphatidylinositol 3-kinase inhibitor

LY-294002 and the ras-raf-mitogen-activated protein kinase inhibitor PD-98059 ($P < 0.002$), which block IGF-I/insulin receptor survival pathways. These observations implicate downregulation of IGF-IR expression in fibroblast apoptosis after alveolar formation.

L11 ANSWER 29 OF 43 MEDLINE on STN DUPLICATE 16

2001511675. PubMed ID: 11559546. Differential insulin-like growth factor I receptor signaling and function in estrogen receptor (ER)-positive MCF-7 and ER-negative MDA-MB-231 breast cancer cells. Bartucci M; Morelli C; Mauro L; Ando' S; Surmacz E. (Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA.) Cancer research, (2001 Sep 15) 61 (18) 6747-54. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The insulin-like growth factor I receptor (IGF-IR) is a ubiquitous and multifunctional tyrosine kinase that has been implicated in breast cancer development. In estrogen receptor (ER)-positive breast tumors, the levels of the IGF-IR and its substrate, insulin-receptor substrate 1 (IRS-1), are often elevated, and these characteristics have been linked with increased radioresistance and cancer recurrence. In vitro, activation of the IGF-IR/IRS-1 pathway in ER-positive cells improves growth and counteracts apoptosis induced by anticancer treatments. The function of the IGF-IR in hormone-independent breast cancer is not clear. ER-negative breast cancer cells often express low levels of the IGF-IR and fail to respond to IGF-I with mitogenesis. On the other hand, **anti-IGF-IR** strategies effectively reduced metastatic potential of different ER-negative cell lines, suggesting a role of this receptor in late stages of the disease. Here we examined IGF-IR signaling and function in ER-negative MDA-MB-231 breast cancer cells and their IGF-IR-overexpressing derivatives. We demonstrated that IGF-I acts as a chemoattractant for these cells. The extent of IGF-I-induced migration reflected IGF-IR levels and required the activation of phosphatidylinositol 3-kinase (PI-3K) and p38 kinases. The same pathways promoted IGF-I-dependent motility in ER-positive MCF-7 cells. In contrast with the positive effects on cell migration, IGF-I was unable to stimulate growth or improve survival in MDA-MB-231 cells, whereas it induced mitogenic and antiapoptotic effects in MCF-7 cells. Moreover, IGF-I partially restored growth in ER-positive cells treated with PI-3K and ERK1/ERK2 inhibitors, whereas it had no protective effects in ER-negative cells. The impaired IGF-I growth response of ER-negative cells was not caused by a low IGF-IR expression, defective IGF-IR tyrosine phosphorylation, or improper tyrosine phosphorylation of IRS-1. Also, the acute (15-min) IGF-I activation of PI-3 and Akt kinases was similar in ER-negative and ER-positive cells. However, a chronic (2-day) IGF-I exposure induced the PI-3K/Akt pathway only in MCF-7 cells. The reactivation of this pathway in ER-negative cells by overexpression of constitutively active Akt mutants was not sufficient to significantly improve proliferation or survival (with or without IGF-I), which indicated that other pathways are also required to support these functions. Our results suggest that in breast cancer cells, IGF-IR can control nonmitogenic processes regardless of the ER status, whereas IGF-IR growth-related functions may depend on ER expression.

L11 ANSWER 30 OF 43 EMBASE

2001188736 EMBASE The receptor for the type I insulin-like growth factor and its ligands regulate multiple cellular functions that impact on metastasis. Samani A.A.; Brodt P.. Dr. P. Brodt, McGill University Health Centre, Division of Surgical Research, Royal Victoria Hospital, 687 Pine Avenue, Montreal, Que. H3A 1A1, Canada. pnina.brodt@muhc.mcgill.ca. Surgical Oncology Clinics of North America Vol. 10, No. 2, pp. 289-312 2001.
Refs: 171.
ISSN: 1055-3207. CODEN: SOCAF7
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20010614

AB Several approaches that were developed recently for suppression of IGF-IR expression and function have already yielded promising results in preclinical studies. Among them are the inhibition of IGF-IR, IGF-I, IGF-II, and IGF binding protein synthesis by antisense oligodeoxynucleotides and the use of antisense expressing vectors for stable expression of IGF-IR or ligand antisense RNA. These approaches lead to inhibition of tumor growth and the induction of apoptosis in a wide range of tumor models including glioblastoma.(97, 137, 162) neuroblastoma,(90) melanoma,(136) teratocarcinoma,(156) osteosarcoma,(71) mesothelioma,(119, 120) hemangiopericytoma,[121] hepatoma,(36, 79) rhabdomyosarcoma.(149) and ovarian,(107) prostate,(12) breast,(21, 110) lung,(81) and cervical(109) carcinomas. In addition, the use of **anti IGF-IR** antibodies (68, 87) and peptide analogues of IGF-I(128) also were effective in reducing tumor cell growth. Effective inhibition of IGF-IR functions also was achieved in several laboratories through the use of IGF-I receptor or IRS-1 dominant negative mutants(13, 62, 67, 133) and by overexpression of a soluble receptor mutant.(29) In a clinical setting, where micrometastases have either been diagnosed or are suspected, the success of IGF-IR directed molecular therapy depends on the availability of highly efficient vehicles for delivery of genetic material into the tumor cells. IGF-IR-directed therapy may be particularly suitable for treatment of metastases in organs such as the liver because normal liver parenchymal cells do not constitutively express measurable levels of IGF-IR. In view of the multiple roles that this receptor plays in tumorigenicity and progression in a wide range of malignancies, its targeting may prove to be a beneficial strategy with global cancer-therapeutic benefits.

L11 ANSWER 31 OF 43 MEDLINE on STN DUPLICATE 17

2001133394. PubMed ID: 11145572. Insulin-like growth factor (IGF) binding protein-3 inhibits type 1 IGF receptor activation independently of its IGF binding affinity. Ricort J M; Binoux M. (Institut National de la Sante et de la Recherche Medicale, Unite 515, Croissance, Differenciation et Processus tumoraux, Hopital Saint-Antoine, Paris, France.) Endocrinology, (2001 Jan) 142 (1) 108-13. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB Insulin-like growth factor binding proteins (IGFBPs) regulate the cellular actions of the IGFs owing to their strong affinities, which are equal to or stronger than the affinity of the type 1 IGF receptor (IGF-IR), the mediator of IGF signal transduction. We recently found that IGFBP-3 modulates IGF-I binding to its receptor via a different mechanism possibly involving conformational alteration of the receptor. We have now investigated the effects of IGFBP-3 on the initial steps in the IGF signaling pathway. MCF-7 breast carcinoma cells were preincubated with increasing concentrations of IGFBP-3 and then stimulated with IGF-I, des(1-3)IGF-I, or [Q(3)A(4)Y(15)L(16)]-IGF-I, the latter two being IGF-I analogs with intact affinity for the type 1 IGF receptor, but weak or virtually no affinity for IGFBPs. Stimulation of autophosphorylation of the receptor and its tyrosine kinase activity was dose-dependently depressed. At 2.5 nM, IGFBP-3 provoked more than 50% inhibition of the stimulation induced by 3 nM des(1-3)IGF-1 and, at 10 nM, more than 80% inhibition. Similar results were obtained with [Q(3)A(4)Y(15)L(16)]-IGF-I. Cross-linking experiments using iodinated or unlabeled IGFBP-3 and **anti-IGF-IR** antibodies indicated that the inhibitory effects do not involve direct interaction between IGFBP-3 and IGF-IR. The inhibition appeared to be specific to IGFBP-3, because IGFBP-1 and IGFBP-5 at 10 nM had no significant effect. Also, inhibition was restricted to the IGF receptor, because IGFBP-3 failed to inhibit the tyrosine kinase activity of the insulin receptor stimulated by physiological concentrations of insulin. Our results provide the first demonstration that IGFBP-3 can specifically modulate the IGF-I signaling pathway independently of its IGF-I-binding ability. They also reveal a regulatory mechanism specific to the type 1 IGF receptor, with no effect on insulin receptor activation.

L11 ANSWER 32 OF 43 MEDLINE on STN DUPLICATE 18
2000250434. PubMed ID: 10791772. Function of the IGF-I receptor in breast cancer. Surmacz E. (Kimmel Cancer Institute, Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA.. surmacz1@jeflin.tju.edu) . Journal of mammary gland biology and neoplasia, (2000 Jan) 5 (1) 95-105. Ref: 58. Journal code: 9601804. ISSN: 1083-3021. Pub. country: United States. Language: English.

AB The insulin-like growth factor-I receptor (IGF-IR) is a transmembrane tyrosine kinase regulating various biological processes such as proliferation, survival, transformation, differentiation, cell-cell and cell-substrate interactions. Different signaling pathways may underlie these pleiotropic effects. The specific pathways engaged depend on the number of activated IGF-IRs, availability of intracellular signal transducers, the action of negative regulators, and is influenced by extracellular modulators. Experimental and clinical data implicate the IGF-IR in breast cancer etiology. There is strong evidence linking hyperactivation of the IGF-IR with the early stages of breast cancer. In primary breast tumors, the IGF-IR is overexpressed and hyperphosphorylated, which correlates with radio-resistance and tumor recurrence. In vitro, the IGF-IR is often required for mitogenesis and transformation, and its overexpression or activation counteract effects of various pro-apoptotic treatments. In hormone-responsive breast cancer cells, IGF-IR function is strongly linked with estrogen receptor (ER) action. The IGF-IR and the ER are co-expressed in breast tumors. Moreover, estrogens stimulate the expression of the IGF-IR and its major signaling substrate IRS-1, while antiestrogens downregulate IGF-IR signaling, mainly by decreasing IRS-1 expression and function. On the other hand, overexpression of IRS-1 promotes estrogen-independence for growth and transformation. In ER-negative breast cancer cells, usually displaying a more aggressive phenotype, the levels of the IGF-IR and IRS-1 are often low and IGF is not mitogenic, yet the IGF-IR is still required for metastatic spread. Consequently, IGF-IR function in the late stages of breast cancer remains one of the most important questions to be addressed before rational **anti-IGF-IR** therapies are developed.

L11 ANSWER 33 OF 43 MEDLINE on STN DUPLICATE 19
1998395132. PubMed ID: 9727029. Interaction of human suppressor of cytokine signaling (SOCS)-2 with the insulin-like growth factor-I receptor. Dey B R; Spence S L; Nissley P; Furlanetto R W. (Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.) Journal of biological chemistry, (1998 Sep 11) 273 (37) 24095-101. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB SOCS (suppressor of cytokine signaling) proteins have been shown to be negative regulators of cytokine receptor signaling via the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. We have cloned a member of this family (hSOCS-2) by utilizing the insulin-like growth factor I receptor (IGF-IR) cytoplasmic domain as bait in a yeast two-hybrid screen of a human fetal brain library. The hSOCS-2 protein interacted strongly with the activated IGF-IR and not with a kinase negative mutant receptor in the two-hybrid assay. Mutation of receptor tyrosines 950, 1250, 1251, and 1316 to phenylalanine or deletion of the COOH-terminal 93 amino acids did not result in decreased interaction of the receptor with hSOCS-2 protein. hSOCS-1 protein also interacted strongly with IGF-IR in the two-hybrid assay. Glutathione S-transferase-hSOCS-2 associated with activated IGF-IR in lysates of mouse fibroblasts overexpressing IGF-IR. Human embryonic kidney cells (293) were transiently transfected with vectors containing IGF-IR and FLAG epitope-tagged hSOCS-2. After IGF-I stimulation, activated IGF-IR was found in anti-FLAG immunoprecipitates and, conversely, FLAG-hSOCS-2 was found in **anti IGF-IR** immunoprecipitates.
Thus, hSOCS-2 interacted with IGF-IR both in vitro and in vivo. HSOCS-2 mRNA was expressed in many human fetal and adult tissues with particularly high abundance in fetal kidney and adult heart, skeletal muscle, pancreas,

and liver. These results raise the possibility that SOCS proteins may also play a regulatory role in IGF-I receptor signaling.

L11 ANSWER 34 OF 43 MEDLINE on STN DUPLICATE 20
1998389421. PubMed ID: 9724028. Deficient processing and activity of type I insulin-like growth factor receptor in the furin-deficient LoVo-C5 cells. Lehmann M; Andre F; Bellan C; Remacle-Bonnet M; Garrouste F; Parat F; Lissitsky J C; Marvaldi J; Pommier G. (Unite Interactions entre Systemes Proteiques et Differenciation dans la Cellule Tumorale, UPRES-A CNRS 6032, Universite d'Aix-Marseille I, Faculte de Pharmacie, France.) Endocrinology, (1998 Sep) 139 (9) 3763-71. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.
AB To investigate endoproteolytic processing of the type I insulin-like growth factor receptor (IGF-IR), we have examined its structure and activity in the furin-deficient LoVo-C5 cell line. Immunoprecipitation experiments using the monoclonal **anti-IGF-IR** antibody (alpha-IR3) showed that LoVo-C5 cells expressed a major high molecular mass receptor (200 kDa) corresponding to the unprocessed alpha/beta pro-receptor. A small amount of successfully cleaved alpha/beta heterodimers was also produced, indicating a residual endoproteolytic cleavage activity in these cells. In vitro, a soluble form of recombinant furin was able to cleave the pro-IGF-IR (200 kDa) into alpha-subunit (130 kDa) and beta-subunit (97 kDa). Measurement of IGF binding parameters in LoVo-C5 cells indicated a low number of typical type I IGF-binding sites (binding capacity, 5 x 10(3) sites/cell; Kd, 1.9 nM for IGF-I and 7.0 nM for IGF-II). These findings in LoVo-C5 contrast with those in HT29-D4 cells, which have active furin, and where IGF-IR (2.8 x 10(4) sites/cell) was fully processed. Moreover, the 200-kDa pro-IGF-IR of LoVo-C5 was unable to induce intracellular signaling, such as beta-subunit tyrosine autophosphorylation and insulin-related substrate-1 tyrosine phosphorylation. Flow immunocytometry analysis using alpha-IR3 antibody indicated that LoVo-C5 cells expressed 40% more receptors than HT29-D4 cells, suggesting that in LoVo-C5 cells only the small amount of mature type I IGF-IR binds IGFs with high affinity. To provide evidence for this idea, we showed that mild trypsin treatment of living LoVo-C5 cells partially restored alpha/beta cleavage of IGF-IR, and greatly enhanced (6-fold) the IGF-I binding capacity of LoVo-C5 cells, but did not restore IGF-IR signaling activity. Moreover, LoVo-C5 cells were totally unresponsive to IGF-I in terms of cell migration, in contrast to fully processed IGF-IR-HT29-D4 cells. Our data indicate that furin is involved in the endoproteolytic processing of the IGF-IR and suggest that this posttranslational event might be crucial for its ligand binding and signaling activities. However, our data do not exclude that other proprotein convertases could participate to IGF-IR maturation.

L11 ANSWER 35 OF 43 MEDLINE on STN DUPLICATE 21
97462728. PubMed ID: 9322955. Insulin-like growth factors I and II are autocrine factors in stimulating proteoglycan synthesis, a marker of differentiated chondrocytes, acting through their respective receptors on a clonal human chondrosarcoma-derived chondrocyte cell line, HCS-2/8. Takigawa M; Okawa T; Pan H; Aoki C; Takahashi K; Zue J; Suzuki F; Kinoshita A. (Department of Biochemistry and Molecular Dentistry, Okayama University Dental School, Japan.. takigawa@dent.okayama-u.ac.jp) . Endocrinology, (1997 Oct) 138 (10) 4390-400. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.
AB Both insulin-like growth factor (IGF)-I and IGF-II increased the synthesis of cartilage-type, large proteoglycan in a human chondrosarcoma-derived chondrocyte cell line, HCS-2/8. In contrast to the stimulatory effects of IGFs on costal chondrocytes of the young rabbit, the stimulatory effect of IGF-II on proteoglycan synthesis in HCS-2/8 cells was more potent than that of IGF-I. IGF-II, but not IGF-I, increased calcium influx into HCS-2/8 cells, and there was a close relation between the stimulation of proteoglycan synthesis and the calcium influx. [125I]IGF-I bound to HCS-2/8 cells, and this binding was competitively inhibited by low concentrations of unlabeled IGF-I, higher concentrations of IGF-II, and

much higher concentrations of insulin. [125I]IGF-II also bound to the cells, and its binding was competitively inhibited by IGF-II and slightly inhibited by higher concentrations of IGF-I and much higher concentrations of insulin. When radioligand-receptor complexes were separated by SDS-PAGE and subjected to autoradiography, two major bands at 260 and 130 kDa were observed, which correspond to the IGF type II receptor (IGF-IIR) and the alpha subunit of the IGF type I receptor (IGF-IR), indicating the presence of both receptors. When confluent cultures of HCS-2/8 cells were maintained in serum-free medium, proteoglycan synthesis did not decrease unless the medium was repeatedly replaced. Conditioned medium of HCS-2/8 cells stimulated the HCS-2/8 cells to synthesize proteoglycans. RIA revealed that the cells produced both IGF-II and IGF-I. Transcripts of messenger RNAs of both IGF-I and IGF-II and both IGF-IR and IGF-IIR also were detectable by Northern analysis. Both **anti-IGF-IR** antibody and anti-IGF-II antibody inhibited proteoglycan synthesis. Mannose-6-phosphate, which is known to bind to IGF-IIR, stimulated proteoglycan synthesis, potentiated IGF-II-stimulated proteoglycan synthesis, and enhanced the binding affinity for IGF-II but not for IGF-I. Even in the presence of **anti-IGF-IR** antibody, IGF-II and mannose-6-phosphate stimulated proteoglycan synthesis in the cells. [Leu27]IGF-II, an IGF-II analogue with high affinity only for IGF-IIR, strongly stimulated proteoglycan synthesis in HCS-2/8 cells but [Arg54, Arg55]IGF-II, which binds to only IGF-IR, also stimulated proteoglycan synthesis in the cells. These findings indicate that IGF-I and IGF-II act as autocrine differentiation factors for this chondrocytic permanent cell line, HCS-2/8, mainly via respective receptors.

L11 ANSWER 36 OF 43 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1998:42698 Document No.: PREV199800042698. Crystallization of the first three domains of the human insulin-like growth factor-1 receptor. McKern, Neil M.; Lou, Meizhen; Frenkel, Maurice J.; Verkuylen, Amanda; Bentley, John D.; Lovrecz, George O.; Ivancic, Neva; Elleman, Thomas C.; Garrett, Thomas P. J.; Cosgrove, Leah J.; Ward, Colin W. [Reprint author]. CSIRO, Div. Mol. Sci., 343 Royal Parade, Parkville, VIC 3052, Australia. Protein Science, (Dec., 1997) Vol. 6, No. 12, pp. 2663-2666. print. ISSN: 0961-8368. Language: English.

AB The insulin-like growth factor-1 receptor (IGF-1R) is a tyrosine kinase receptor of central importance in cell proliferation. A fragment (residues 1-462) comprising the L1-cysteine rich-L2 domains of the human IGF-1R ectodomain has been overexpressed in glycosylation-deficient Lec8 cells and has been affinity-purified via a c-myc tag followed by gel filtration. The fragment was recognized by two **anti-IGF-IR** monoclonal antibodies, 24-31 and 24-60, but showed no detectable binding of IGF-1 or IGF-2. Isocratic elution of IGF-1R/462 on anion-exchange chromatography reduced sample heterogeneity, permitting the production of crystals that diffracted to 2.6 ANG resolution with cell dimensions a 77.0 ANG, b = 99.5 ANG, c = 120.1 ANG and space group P212121.

L11 ANSWER 37 OF 43 MEDLINE on STN DUPLICATE 22

97266659. PubMed ID: 9112401. Up-regulation of insulin/insulin-like growth factor-I hybrid receptors during differentiation of HT29-D4 human colonic carcinoma cells. Garrouste F L; Remacle-Bonnet M M; Lehmann M M; Marvaldi J L; Pommier G J. (Unite Interactions entre Systemes Proteiques et Differenciation dans la Cellule Tumorale, CNRS URA 1924, Faculte de Medecine, Marseille, France.) Endocrinology, (1997 May) 138 (5) 2021-32. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB To assess the autocrine function of insulin-like growth factor II (IGF-II) in the balance of proliferation and differentiation in HT29-D4 human colonic cancer cells, we studied the expression of IGF-I receptors (IGF-IR) and insulin receptors (IR) in relation to the state of cell differentiation. IGF-IR and IR were expressed in both undifferentiated

and enterocyte-like differentiated HT29-D4 cells. IGF-IR had two isoforms with a 97-kDa and a 102-kDa beta-subunit. In addition, HT29-D4 cells expressed hybrid receptors (HR) formed by the association of two alphabeta heterodimers from both IR and IGF-IR. HR were evidenced through 1) inhibition of IGF-I binding by the B6 anti-IR antibody and 2) immunoprecipitation with the alpha-IR3 **anti-IGF-IR** antibody, which revealed an additional 95-kDa IR beta-subunit that disappeared when the heterotetrameric receptor was dissociated by disulfide reduction into alphabeta heterodimers before immunoprecipitation. Like IGF-IR, HR had a high affinity for IGF-I (Kd, approximately 1.5 nM), but did not bind insulin significantly; the latter interacted with the native IR only (Kd, approximately 4 nM). In the differentiated HT29-D4 cell monolayer, all receptor species were strongly polarized (>97%) toward the basolateral membrane. Moreover, HT29-D4 cell differentiation was accompanied by an approximately 2-fold increase in the number of IR, whereas the number of IGF-I-binding sites was unaltered. However, in differentiated HT29-D4 cells, approximately 55% of the latter were involved in HR vs. approximately 20% in undifferentiated HT29-D4 cells. Thus, HT29-D4 cell differentiation is characterized by an up-regulation (approximately 3-fold) of the level of HR coupled to a down-regulation (approximately 40%) of the level of native tetrameric IGF-IR. Alterations were induced early during the cell differentiation process, i.e. 5 days postconfluence, and remained unchanged for at least 21 days. Taken together, these results suggest that the IGF-II autocrine loop in HT29-D4 cells may trigger distinct signaling pathways if it activates native IGF-IR, which predominate in undifferentiated cells, or if it activates HR, which are up-regulated in differentiated cells.

L11 ANSWER 38 OF 43 MEDLINE on STN DUPLICATE 23

97131968. PubMed ID: 8977425. Regulation of myeloid growth and differentiation by the insulin-like growth factor I receptor. Li Y M; Schacher D H; Liu Q; Arkins S; Rebeiz N; McCusker R H Jr; Dantzer R; Kelley K W. (Laboratory of Immunophysiology, University of Illinois, Urbana 61801, USA.) Endocrinology, (1997 Jan) 138 (1) 362-8. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB Flow cytometry was used to examine the expression of type I insulin-like growth factor receptors (IGF-IR) on three types of human hematopoietic cells that represent different stages of myeloid lineage development. Both HL-60 (promyeloid) and U-937 (monocytic) cells express abundant IGF-IR protein (> 79% cells positive for the IGF-IR), whereas KG-1 myeloblasts express negligible levels of IGF-IR (< 1% IGF-IR-positive cells). Exogenous IGF-I, IGF-II, and an IGF-I analog that binds poorly to IGF-binding protein-3 (des-IGF-I) increased DNA synthesis of HL-60 and U-937 cells in a dose-dependent (1-25 ng/ml) fashion by 2- to 4-fold in serum-free medium, whereas KG-1 cells did not respond to any of these growth factors. The IGF-induced increase in proliferation of HL-60 promyeloid cells was inhibited by soluble IGF-binding protein-3 (500 ng/ml) when these cells were stimulated with 10 ng/ml of either IGF-I (53 +/- 8%) or IGF-II (59 +/- 8%), but not with des-IGF-I (3 +/- 1%). In contrast, the **anti-IGF-IR** monoclonal antibody (mAb; alpha IR-3) inhibited the DNA synthesis caused by 10 ng/ml exogenous IGF-I (67 +/- 6%), IGF-II (72 +/- 8%), and des-IGF-1 (82 +/- 9%). Proliferation of KG-1 myeloblasts, however, was neither stimulated by the IGFs nor inhibited by the **anti-IGF-IR** mAb. In the absence of exogenous IGF-I, the mAb directed against the IGF-IR significantly suppressed basal DNA synthesis of HL-60 promyeloid (72 +/- 5%) and U-937 monocytic (39 +/- 7%) cells, but did not affect DNA synthesis of KG-1 myeloblasts (8 +/- 1%) compared to an isotype-matched control mAb. Similarly, the alpha IR-3 mAb abrogated vitamin D3-induced differentiation of the HL-60 cells into macrophages in serum-free medium, as assessed by expression of the leucam surface protein, CD11b. As the alpha IR-3 mAb inhibits DNA synthesis in the presence and absence of exogenous IGF-I on receptor-bearing cells, but not IGF-IR-negative cells, these data demonstrate that both endocrine and autocrine IGF-I are potent

growth factors in human myeloid cells where expression of the surface receptor, rather than the ligand, is the critical control element. More importantly, these data support the hypothesis that autocrine IGF-I may play a significant role in the differentiation of promyeloid cells into macrophages.

L11 ANSWER 39 OF 43 MEDLINE on STN DUPLICATE 24
1998113984. PubMed ID: 9453239. Increased abundance of insulin/IGF-I hybrid receptors in adipose tissue from NIDDM patients. Federici M; Porzio O; Zucaro L; Giovannone B; Borboni P; Marini M A; Lauro D; Sesti G. (Department of Internal Medicine, University of Rome-Tor Vergata, Italy.) Molecular and cellular endocrinology, (1997 Nov 30) 135 (1) 41-7. Journal code: 7500844. ISSN: 0303-7207. Pub. country: Ireland. Language: English.
AB Insulin/IGF-I hybrid receptors composed of an insulin receptor (IR) alphabeta-hemireceptor and a type 1 IGF receptor (IGF-IR) alphabeta-hemireceptor are formed in tissues expressing both molecules. To date there is a limited information about the proportion of hybrids in tissues of normal or diabetic subjects. In this study, we determined the abundance of hybrids in fat from control and NIDDM subjects by using a microwell-based immunoassay. Microwells coated with MA-20 anti-IR or alpha-IGF-IR-PA **anti-IGF-IR** antibody were incubated with tissue extracts. Immunoadsorbed receptors were incubated with 125I-insulin or 125I-IGF-I in the presence or absence of unlabeled ligands, and hybrids were quantitated as the fraction of 125I-IGF-I binding immunoadsorbed with MA-20. Abundance of hybrids was increased in NIDDM patients as compared with controls (B/T = 1.29 +/- 0.18 and 0.52 +/- 0.06%; P < 0.008, respectively), and it was inversely correlated with both IR number (r = -0.65; P < 0.002), and in vivo insulin sensitivity measured by insulin tolerance test (r = -0.75; P < 0.005), whereas it was positively correlated with insulinemia (r = 0.63; P < 0.003). Insulin binding affinity was lower in NIDDM subjects than in controls (ED50 = 1.87 +/- 0.32 and 0.54 +/- 0.20 nmol/l; P < 0.009, respectively), and was correlated with the percentage of hybrids. Maximal IGF-I binding was significantly greater in NIDDM patients than controls and was positively correlated with the percentage of hybrids whereas IGF-I binding affinity did not differ between the two groups. Results show that expression of hybrids is increased in fat of NIDDM patients compared to control subjects and is correlated with in vivo insulin sensitivity thus raising the possibility that alterations in expression of hybrids which bind IGF-I with higher affinity than insulin may contribute, at least in part, to insulin resistance.

L11 ANSWER 40 OF 43 MEDLINE on STN DUPLICATE 25
96285603. PubMed ID: 8689633. Inhibition of stilbene estrogen-induced cell proliferation of renal epithelial cells through the modulation of insulin-like growth factor-I receptor expression. Chen C W; Oberley T D; Roy D. (Department of Environmental Health Sciences, University of Alabama at Birmingham 35294-0008, USA.) Cancer letters, (1996 Jul 19) 105 (1) 51-9. Journal code: 7600053. ISSN: 0304-3835. Pub. country: Ireland. Language: English.
AB In the present study, we have investigated the effects of stilbene estrogen, diethylstilbestrol (DES), on the proliferative activity and expression of insulin-like growth factor-I (IGF-I) receptor in Syrian hamster renal epithelial cells. DES exposure to renal epithelial cells caused both dose- and time-dependent increases in proliferative activity. We also tested the effects of antiestrogen ICI 182780 and insulin-like growth factor-I receptor (IGF-IR) antibody on cell proliferation. Cotreatment of cells with ICI 182780 (250 nM) and DES resulted in a 50% decrease in cell growth compared to DES alone. Treatment of cells with an **anti-IGF-IR** antibody (alpha IR3, 1 microgram/ml) also significantly reversed the growth-stimulatory effects of DES. A nuclear binding assay revealed that an enhanced level (approximately 2-fold) of [125I]IGF-I binding to nuclear protein occurred in DES treated renal epithelial cell nuclei compared to controls. IGF-I receptor gene expression analyzed by Northern blotting revealed that DES

treatment increased the level of IGF-IR mRNA by 2-fold compared to controls. We also tested the effect of ICI compound on the induction of IGF-I receptor gene. The cotreatment of ICI 182780 strongly inhibited DES-induced IGF-I receptor gene expression (50-60% inhibition). Stimulation of the proliferative activity of renal epithelial cells by stilbene estrogen, its prevention by IGF-I receptor antibody, and inhibition of DES-induced proliferative activity and the expression of IGF-I receptors by ICI 182780 suggest the possibility that the stimulatory effect of DES on the proliferative activity of renal epithelial cells may be mediated through the up-regulation of IGF-I receptors.

L11 ANSWER 41 OF 43 MEDLINE on STN DUPLICATE 26
95262099. PubMed ID: 7743492. Insulin-like growth factor I overexpression in human pancreatic cancer: evidence for autocrine and paracrine roles. Bergmann U; Funatomi H; Yokoyama M; Beger H G; Korc M. (Department of Medicine, University of California, Irvine 92717, USA.) Cancer research, (1995 May 15) 55 (10) 2007-11. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.
AB We assessed the potential roles of insulin-like growth factor-I (IGF-I) and the IGF-I receptor (IGF-IR) in human pancreatic cancer. IGF-I enhanced the growth of ASPC-1 and COLO-357 human pancreatic cancer cells, and this effect was significantly inhibited by a highly specific monoclonal **anti-IGF-IR** antibody (alpha IR3). Both cell lines expressed mRNA transcripts for IGF-IR, and basal cell growth was significantly reduced by an IGF-IR antisense oligodeoxynucleotide. IGF-I mRNA transcripts were not detected in either cell line or in two additional pancreatic cancer cell lines. In contrast, analysis of 12 pancreatic cancers revealed a 32-fold increase ($P < 0.01$) in IGF-I mRNA levels by comparison with the low levels observed in the normal pancreas. By in situ hybridization, IGF-I mRNA grains were present in both the cancer cells and in the surrounding connective tissue. Six of the cancers exhibited a 4.4-fold increase in IGF-IR mRNA levels. These findings suggest that IGF-I may participate in aberrant autocrine and paracrine activation of IGF-IR in pancreatic cancer in vivo.

L11 ANSWER 42 OF 43 MEDLINE on STN DUPLICATE 27
96042029. PubMed ID: 7589243. Insulin-like growth factor-II as a paracrine growth factor in human neuroblastoma cells. Leventhal P S; Randolph A E; Vesbit T E; Schenone A; Windebank A; Feldman E L. (Department of Neurology, University of Michigan, Ann Arbor 48109-0588, USA.) Experimental cell research, (1995 Nov) 221 (1) 179-86. Journal code: 0373226. ISSN: 0014-4827. Pub. country: United States. Language: English.
AB The human neuroblastoma line, SK-N-SH, has been subcloned into SH-SY5Y, a neuroblast N cell line, and SH-EP, an epithelial Schwann S cell line. We have previously shown that SH-SY5Y neuroblastoma cells produce insulin-like growth factor II (IGF-II), which acts by an autocrine mechanism to stimulate cell growth. In the current study, we examined the effect of IGF-II on SH-EP neuroblastoma cells. Northern blot and reverse transcriptase-polymerase chain reaction analyses indicate that SH-EP cells do not produce IGF-I or IGF-II but express the type I and type II IGF receptors (IGF-IR and IGF-IIR). Cell surface expression of IGF-IR, assessed by fluorescence-activated sorting, was lower in SH-EP cells than in SH-SY5Y cells. Immunoprecipitation of IGF-IR, followed by anti-phosphotyrosine or **anti-IGF-IR** immunoblotting, demonstrated functional expression of these receptors in both cell types and confirmed the lower level of IGF-IR expression in SH-EP cells. IGF-II promoted SH-EP cell growth in the presence of low concentrations of calf serum (0.1-0.3%) or 10 ng/ml epidermal growth factor (EGF). IGF-II stimulation of SH-EP growth was eliminated by the IGF-IR blocking antibody (alpha IR-3) but not by an IGF-IIR blocking antibody. Stimulation of cell growth via this receptor was also indicated by the ligand specificity for IGF analogs and insulin (IGF-II approximately IGF-I approximately des(1-3)IGF-I >> insulin). These results indicate that in the presence of a permissive factor such as calf serum or EGF, IGF-II stimulates SH-EP cell growth via the IGF-IR.

Collectively, these data suggest that within primary neuroblastomas, IGF-II may act as a paracrine factor to contribute to the promotion of S cell growth.

L11 ANSWER 43 OF 43 MEDLINE on STN DUPLICATE 28
94133531. PubMed ID: 8301926. Distribution and relevance of insulin-like growth factor-I receptor in metanephric development. Liu Z Z; Wada J; Alvares K; Kumar A; Wallner E I; Kanwar Y S. (Department of Pathology, Northwestern University Medical School, Chicago, Illinois.) Kidney international, (1993 Dec) 44 (6) 1242-50. Journal code: 0323470. ISSN: 0085-2538. Pub. country: United States. Language: English.
AB During embryogenesis, various ligand-receptor interactions take place to modulate the development and growth of various mammalian organs. During these interactions, a critical concentration of a given receptor is needed to elicit a ligand-induced biologic response at a defined gestational stage of the fetus. In this study, the distribution and the relevance of insulin-like growth factor-I receptor (IGF-IR) in metanephric development was investigated. Kidneys were harvested from mouse embryos at days 13 to 19 of fetal gestation, and maintained in a metanephric culture system. Immunofluorescence studies, using **anti-IGF-IR** , revealed a high expression of IGF-IR at day 13, which declined during the later stages of gestation through neonatal life. To study the relevance of IGF-IR expression in metanephric development, antisense-oligodeoxynucleotide (ODN) experiments were carried out. Antisense-ODN 43 mer probes were synthesized utilizing rat IGF-IR cDNA selected nucleotide sequences which are highly conserved in other mammalian species. Southern blot analyses of various restriction fragments of the rat and mice genomic DNA yielded similar bands when hybridized with the antisense-ODN or rat IGF-IR cDNA, suggesting a high degree of homology in the region of the gene selected for the synthesis of antisense-ODN. Also, the antisense-ODN hybridized with the appropriate murine fetal kidney mRNA species, as ascertained by S1 nuclease protection assay. Inclusion of antisense-ODN in the culture medium resulted in an inhibition of the growth of the kidney, reduction in the population of the nephrons and disorganization of the ureteric bud branches.(ABSTRACT TRUNCATED AT 250 WORDS)

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L13 5326 (GOETSCH L?/AU OR CORVAIA N?/AU OR LEGER O?/AU OR DUFLOS A?/AU OR HAEUW J?/AU OR BECK A?/AU)

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L15 7 L14 AND INSULIN-LIKE GROWTH FACTOR I RECEPTOR

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L16 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
2005:1200829 Document No. 143:458527 **Antibodies** to the human **insulin-like growth factor I receptor** (IGF-IR) and/or to insulin/IGF-I hybrid receptors and anticancer and diagnostic uses thereof. **Goetsch, Liliane; Corvaia, Nathalie; Duflos, Alain; Haeuw, Jean-Francois; Leger, Olivier; Beck, Alain** (Pierre Fabre Medicament, Fr.). U.S. Pat. Appl. Publ. US 2005249730 A1 20051110, 144 pp., Cont.-in-part of U.S. Ser. No. 735,916. (English). CODEN: USXXCO. APPLICATION: US 2004-12353 20041216. PRIORITY: FR

2002-654 20020118; FR 2002-653 20020118; FR 2002-5753 20020507; WO 2003-FR178 20030120; FR 2003-8538 20030711; US 2003-2003/735916 20031216.

AB The present invention relates to novel **antibodies** capable of binding specifically to the human **insulin-like growth factor I receptor** (IGF-IR) and/or the insulin/IGF-I hybrid receptor (hybrid-R) and/or capable of specifically inhibiting the tyrosine kinase activity of said IGF-IR and/or hybrid-R, especially monoclonal **antibodies** of murine, chimeric and humanized origin, as well as the amino acid and nucleic acid sequences coding for these **antibodies.** Provided are protein and cDNA sequences for anti-IGF-IR and/or anti-insulin/IGF-I hybrid receptors **antibodies.** The invention likewise comprises the use of these **antibodies** as a medicament for the prophylactic and/or therapeutic treatment of cancers overexpressing IGF-IR and/or hybrid-R or any pathol. connected with the overexpression of said receptor as well as in processes or kits for diagnosis of illnesses connected with the overexpression of the IGF-IR and/or hybrid-R. The invention finally comprises products and/or compns. comprising such **antibodies** in combination with anti-EGFR **antibodies** and/or compds. and/or anti-cancer agents or agents conjugated with toxins and their use for the prevention and/or the treatment of certain cancers.

L16 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

2005:346710 Document No. 142:390956 **Antibodies** to **insulin -like growth factor I receptor. Goetsch, Liliane; Corvaia, Nathalie ; Leger, Olivier; Duflos, Alain; Haeuw, Jean-francois; Beck, Alain** (Fr.). U.S. Pat. Appl. Publ. US 2005084906 A1 20050421, 125 pp., Cont.-in-part of Appl. No. PCT/FR03/00178. (English). CODEN: USXXCO. APPLICATION: US 2003-735916 20031216. PRIORITY: FR 2002-654 20020118; FR 2002-653 20020118; FR 2002-5753 20020507; WO 2003-FR178 20030120; FR 2003-8538 20030711.

AB The authors disclose **antibodies** capable of binding specifically to the human **insulin-like growth factor I receptor** (IGF-IR) and/or capable of specifically inhibiting the IGF-IR tyrosine kinase activity. The monoclonal **antibodies** are of murine, chimeric and humanized origin **antibodies** and can be used as a medicament for the prophylactic and/or therapeutic treatment of cancers overexpressing IGF-IR or any pathol. connected with the IGF-IR overexpression. Addnl., the authors disclose the use of these **antibodies** in combination with anti-EGFR **antibodies** and/or anti-cancer agents or agents conjugated with toxins and their use for the prevention and/or the treatment of certain cancers.

L16 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

2004:1120703 Document No. 142:174952 A recombinant humanized anti-insulin-like growth factor receptor type I **antibody** (h7C10) enhances the antitumor activity of vinorelbine and anti-epidermal growth factor receptor therapy against human cancer xenografts. **Goetsch, Liliane**; Gonzalez, Alexandra; **Leger, Olivier**; **Beck, Alain**; Pauwels, Petrus J.; **Haeuw, Jean Francois**; **Corvaia, Nathalie** (Centre d'Immunologie Pierre Fabre, St. Julien en Genevois, Fr.). International Journal of Cancer, 113(2), 316-328 (English) 2005. CODEN: IJCNAW. ISSN: 0020-7136. Publisher: Wiley-Liss, Inc..

AB Interaction of insulin-like growth factor receptor I (IGF-IR) with its ligands has been reported to induce cell proliferation, transformation, and blockade of cell apoptotic functions. IGF-IR is overexpressed on numerous tumor cell types and its blockade could be of importance for anti-cancer therapy. We have generated a humanized anti-IGF-IR **antibody** h7C10 that blocks in vitro IGF-I and IGF-II-induced cell proliferation of MCF-7 breast cancer cells. Anal. of the IGF-I transduction cascade demonstrated that the humanized anti-IGF-IR **antibody** and its murine parental form block IGF-I-induced tyrosine

phosphorylation, both its β-chain and IRS-1 tyrosine phosphorylation. This presumably leads to cell cycle arrest and, consequently, growth inhibition. Treatment of nude mice bearing either human breast cancer cells (MCF-7) or non small lung cancer cells (A549) with h7C10, or its murine parental form 7C10, inhibited significantly tumor growth. An almost complete inhibition of A549 tumor growth was observed when mice were treated with the anti-IGF-IR **antibody** combined with either a chemotherapeutic agent, Vinorelbine or an anti-epidermal growth factor receptor (EGFR) **antibody**, 225. Combined therapy prolonged significantly the life span of mice in an orthotopic in vivo model of A549; the combination of the anti-IGF-IR **antibody** with an anti-EGFR **antibody** was superior to the Vinorelbine combination. The present results indicate that the humanized anti-IGF-IR **antibody** h7C10 has a great potential for cancer therapy when combined with either a chemotherapeutic agent or an **antibody** that targets other growth factor receptors, such as the epidermal growth factor receptor.

L16 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

2005:319273 Document No. 142:409414 Characterization by liquid chromatography combined with mass spectrometry of monoclonal anti-IGF-1 receptor **antibodies** produced in CHO and NS0 cells. **Beck, Alain**; Bussat, Marie-Claire; Zorn, Nathalie; Robillard, Virginie; Klinguer-Hamour, Christine; Chenu, Stephane; **Goetsch, Liliane**; **Corvaia, Nathalie**; Van Dorsselaer, Alain; **Haeuw, Jean-Francois** (Centre d'Immunologie Pierre Fabre (CIPF), Saint-Julien-en-Genevois, 74160, Fr.). Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences, 819(2), 203-218 (English) 2005. CODEN: JCBAAI. ISSN: 1570-0232. Publisher: Elsevier B.V..

AB 7H2HM is a new humanized recombinant monoclonal **antibody** (MAb) directed against insulin-like growth factor-1 receptor and produced in CHO cells. Homogeneity of intact **antibody**, reduced light and heavy chains, Fab and Fc fragments were investigated by anal. methods based on mass (SDS-PAGE, SEC), charge (IEF, C-IEX) and hydrophobicity differences (RP-HPLC, HIC) and compared side-by-side with A2CHM, produced in NS0 cells. Primary structures and disulfide bridge pairing were analyzed by microsequencing (Edman degradation), mass spectrometry (MALDI-TOF, ES-TOF) and peptide mapping after enzymic digestion (Trypsin, endoprotease Lys-C, papain). The light chains demonstrated the expected sequences. The heavy chains yielded post-translational modifications previously reported for other recombinant humanized or human IgG1 such as N-terminal pyroglutamic acid, C-terminal lysine clipping and N-glycosylation for asparagine 297. More surprisingly, two-thirds of the 7H2HM heavy chains were shown to contain an addnl. 24-amino-acid sequence, corresponding to the translation of an intron located between the variable and the constant domains. These data suggest that 7H2HM is a mixture of three families of **antibodies** corresponding (i) to the expected structure (17%; 149 297 Da; 1330 amino acids), (ii) a variant with a translated intron in one heavy chains (33%; 152 878 Da; 1354 amino acids) and (iii) a variant with translated introns in two heavy chains (50%; 154 459 Da; 1378 amino acids), resp. RP-HPLC is not a commonly used chromatog. method to assess purity of monoclonal **antibodies** but unlike SEC and SDS-PAGE, was able to show and to quantify the family of structures present in 7H2HM, which were also identified by peptide mapping, mass spectrometry and microsequencing.

L16 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

2003:571020 Document No. 139:132446 Monoclonal and humanized **antibodies** to insulin-like growth factor 1 receptors for use in the diagnosis and treatment of disease. **Goetsch, Liliane**; **Corvaia, Nathalie**; **Leger, Olivier** (Pierre Fabre Medicament, Fr.). PCT Int. Appl. WO 2003059951 A2 20030724, 164 pp. DESIGNATED STATES: W: AU, CA, CN, JP, MX, US, ZA; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (French). CODEN: PIXXD2. APPLICATION: WO 2003-FR178 20030120. PRIORITY: US

2002-2002/200653 20020118; US 2002-2002/200654 20020118; US 2002-2002/205753 20020507.

AB The invention relates to novel **antibodies** capable of binding specifically to the human **Insulin-like Growth Factor-I Receptor** (IGF-IR), in particular monoclonal of murine origin, chimeric and humanized as well as the amino and nucleic acid sequences coding for said **antibodies.** The invention also concerns the use of said **antibodies** as medicine for prophylactic and/or therapeutic treatments of cancers as well as methods or kit for diagnosis of diseases related to overexpression of the IGF-IR receptor. The invention further concerns products and/or compns. containing such **antibodies** combined with **antibodies** to epidermal growth factor receptors and/or compds. and/or anti-cancer agents or conjugates with toxins and their use for preventing and/or treating certain cancers.

L16 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

2003:573239 Document No. 139:132447 Monoclonal and humanized **antibodies** to insulin-like growth factor 1 receptors for use in diagnosis and treatment of cancer. **Goetsch, Liliane; Leger, Olivier; Corvaia, Nathalie** (Pierre Fabre Medicament, Fr.). Fr. Demande FR 2834990 A1 20030725, 137 pp. (French). CODEN: FRXXBL. APPLICATION: FR 2002-653 20020118.

AB The invention relates to novel **antibodies** capable of binding specifically to the human **Insulin-like Growth Factor-I Receptor** (IGF-IR), in particular monoclonal of murine origin, chimeric and humanized as well as the amino and nucleic acid sequences coding for said **antibodies.** The invention also concerns the use of said **antibodies** as medicine for prophylactic and/or therapeutic treatments of cancers as well as methods or kit for diagnosis of diseases related to overexpression of the IGF-IR receptor. The invention further concerns products and/or compns. containing such **antibodies** combined with **antibodies** to epidermal growth factor receptors and/or compds. and/or anti-cancer agents or conjugates with toxins and their use for preventing and/or treating certain cancers.

L16 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

2003:573225 Document No. 139:138720 New compositions with anti-IGF-1R and anti-EGFR activity and their applications. **Goetsch, Liliane; Corvaia, Nathalie; Leger, Olivier** (Pierre Fabre Medicament, Fr.). Fr. Demande FR 2834900 A1 20030725, 146 pp. (French). CODEN: FRXXBL. APPLICATION: FR 2002-654 20020118.

AB Compds. are disclosed that can bind to the insulin-like growth factor 1 receptor (IGF-1R) and the epidermal growth factor receptor (EGFR). **Antibodies** specific for these receptors are disclosed, as well as DNAs encoding them. The compds. may be used as antitumor agents as well as diagnostic agents for diagnosing diseases related to overexpression of IGF-1R and EGFR.

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